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BRITISH JOURNAL OF TUBERCULOSIS AND DISEASES OF THE CHEST

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THE RELATIONSHIP OF TUBERCULOSIS TO THE DEVELOPMENT OF MASSIVE PNEUMOKONIOSIS IN COAL WORKERS

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IT has been known for many years that dust accumulation occurs in coal workers' lungs in two forms. Sometimes there are small foci scattered uniformly throughout both lungs. This is simple pneumokoniosis (Fig. 2). In other cases one or both lungs contain much larger dust-laden fibrous lesions, situated usually in the upper parts of the lungs (Fig. 7). This lesion is called coal workers' massive pneumokoniosis or progressive massive fibrosis and its etiology is the subject of dispute. Some authors consider that it can be produced by the effects of dust alone. Others believe that a second factor is essential—probably an infective factor.

The nature of the massive lesion has previously been investigated clinically, pathologically and radiologically and a summary of the findings of previous workers is relevant to an account of the present study. Cox in 1857 reported on the diseases of colliers in south Lancashire. He observed that " tubercular consumption " was frequently met with and postulated that the inhalation of coal dust in some way weakened the lung and contributed to the development of phthisis. He could not, however, support the suggestion that the coal produces serious effects only on those who are already " unsound in the lungs or prone to decline." He considered that the coal dust predisposed to tuberculosis, but believed that the dust could produce serious effects in the absence of an inflammatory factor.

Oliver (1909) considered that serious fibrosis in coal miners was due to the inhalation of stone dust from the roof and floor of the seam, and that it was not caused by the coal dust itself. He regarded the silica content of the dust as the important fibrogenic agent and did not think it necessary to postulate an infective factor.

In 1923 Haldane reported that coal miners had less liability to tuberculosis than other industrial workers. He believed that the inhaled coal dust tended to prevent phthisis. He observed that when pulmonary tuberculosis was present in a coal worker the gross appearance of the lesion differed markedly

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from that seen in non-miners. In some specimens he found it quite difficult to distinguish between chronic tubercles and other lesions which he termed " non-laminated silicotic nodules." He concluded that serious fibrosis was due to silica inhalation and stated as a corollary that, in the absence of the silica factor, South Wales coal workers would not suffer from serious pulmonary fibrosis.

In 1931 Cummins and Weatherall showed that coal dust was capable of altering the effects of tuberculin in experimental animals and gave it as their opinion that massive pneumokoniosis might be a non-caseous benign fibrotic type of tuberculosis.

Amor and Evans in 1934 observed clinically and radiologically that cavitation often occurred in massive pneumokoniosis, and said that under these circumstances there could be little doubt that the case had become complicated by tuberculosis. They implied that tuberculosis was a frequent complication, but they did not regard it as essential to the etiology.

In 1939 Policard *et al.* studied the lungs of twenty miners and noted that nodules were often found. Sometimes the nodules had the appearance of typical active tuberculous foci, but these graded insensibly into fibro-hyaline nodules lacking caseation or other histological evidence of tuberculosis.

Belt and Ferris in 1942 reported on the histological appearances and noted a similarity to those in tuberculosis. They considered that tuberculosis might sometimes be the factor responsible for massive pneumokoniosis.

King and Nagelschmidt in 1945 observed a lack of correlation between the amount of coal and the amount of fibrosis in the lungs. They advanced reasons for accepting quartz as the major etiological agent in the production of the fibrosis.

Gooding in 1946 reported the presence of tuberculosis in 26 per cent. of 230 coal miners at autopsy. He also observed by follow-up studies that in some cases whose sputa had been positive in life tuberculosis could not be demonstrated at post-mortem.

In 1949 McVittie reported on 214 autopsies of men with massive disease and found tuberculosis in 30 per cent.

At a meeting of the Tuberculosis Association in 1946 Rogers gave the following data: Of 831 lung specimens from South Wales miners 35 per cent. showed gross tuberculous lesions. After histological examinations had been made tuberculosis was found in 75 per cent. of the cases with massive disease.

In a special report of the Medical Research Council (1942) Belt describes his examination of 42 lungs affected by massive fibrosis. He found tubercle bacilli in only 8, and in 15 others with lesions of identical appearance he failed to detect the bacillus by staining methods.

Sander (1946) conjectured that dusts of low silica content, such as coal dust, would tend to accumulate round tuberculous lesions and would add to the fibrosis, possibly causing the organisms to die, leaving nothing but a dense overgrowth of fibrous tissue.

In 1937 Gardner described four autopsy cases showing typical gross and microscopic evidence of tuberculous cavitation. Two were negative on guinea-pig inoculation and he believed that in these the organism had initiated the lesion and had since died out.

The disease has frequently been investigated clinically with special reference to its relationship to tuberculosis.

In 1933 Williams examined 100 old retired miners by clinical and hæmatological methods and found evidence of active tuberculosis in 27. She observed four sputum-positive cases in which the tuberculosis was so atypical that it had not been suspected by the family doctors. Gooding made a similar observation in 1946, reporting that some sputum-positive cases of tuberculosis in miners with pneumokoniosis showed no toxic features at all. Both these authors observed that the presence of dust in the lungs often had a profound modifying effect on the clinical manifestations of coexistent tuberculosis.

Sen in 1937 reported on the difficulty of distinguishing radiologically between massive pneumokoniosis and tuberculosis. On the basis of clinical and radiological tests he considered that 35 per cent. of the miners he examined "gave some indication of tuberculosis in a more or less active state." Furthermore, he found 7 miners with definite tuberculosis who had no constitutional symptoms at all.

In the same year, Moore Hall, a general practitioner, found sputum-positive tuberculosis in 11 of a consecutive series of 64 coal miners attending his surgery for chronic chest disease.

A series of 100 miners with chronic chest disease was reported by Jones in 1938. He considered that he was able in some cases to distinguish radiologically between massive pneumokoniosis and chronic tuberculosis. It was his view that tuberculosis was a late complication of the dust disease but that it did not cause the condition.

The problem was approached in a different way by Bedford and Warner in 1943. They related the incidence of "X-ray consolidations" in a series of miners to the dustiness of the pits in which they worked and found that the correlation was good. This would seem to indicate either that the "consolidations" can be produced by the inhalation of a lot of dust, or that such inhalation facilitates the action of a local infective factor.

Stewart in 1948 reported on her study of the disease after dust exposure had ceased. Two of her patients developed cavitation whilst under observation. One had a positive sputum after the event, the other did not. She observed a relationship between the rate of radiological progression of massive disease and the erythrocyte sedimentation rate which suggested that enlargement of the local lesion was associated with infection.

In 1949 Davies *et al.* showed that in the case of men with a moderate degree of simple pneumokoniosis the risk of developing massive disease was not reduced by ceasing exposure to dust. This would suggest that the mass is due either to sufficient dust plus sufficient time or to sufficient dust plus a second factor which is present outside coal mines.

In 1951 Mann reported on his study of serial X-rays in South Wales coal workers. He found that the attack rate of tuberculosis was increased by the presence of simple pneumokoniosis. He also noted that, in comparison with Reisner's series of non-miners, tuberculosis progressed relatively slowly in men with simple pneumokoniosis.

In 1952 Cochrane *et al.* reported on their survey of the tuberculosis incidence in the Rhondda Fach. They found the incidence in the male general population

to be highest at the age of 55, when it was 1·2 per cent. A similar incidence of open tuberculosis was found in miners with massive pneumokoniosis. The incidence in young miners age 25 to 34 was high, being 3·7 per cent.

The difficulty of distinguishing between massive disease and tuberculosis is not removed by radiography.

In 1938 Jones reported on the similar radiographic appearance and commented that the only solution lay in autopsy investigation of a large series of cases.

In a 1941 Bulletin of the U.S. Public Health Service the same difficulty is emphasised, the authors admitting that it was sometimes impossible to distinguish radiologically between the two conditions.

In 1948 Fletcher reported on his study of the progress of cases of simple pneumokoniosis to massive disease. He noticed that a minority developed localised coalescent mottling without an intervening stage of generalised mottling and that once the localised mottling had occurred progression to massive shadows was the rule.

Cochrane *et al.* considered that in miners with pneumokoniosis massive fibrosis and tuberculosis were radiologically indistinguishable.

During the period 1947 to 1950 autopsies were made by the author on 1,000 South Wales coal workers.

The series was in some degree a selected one. A case would come to autopsy if a relative, on medical advice, notified the coroner that it was believed that the death was in some way related to pneumokoniosis. Hence the majority had suffered from chronic dyspnœa. Two types of case would be less likely to come to post-mortem:

(1) Those to whom compensation had been paid in the form of a lump sum which precluded any payment of benefit to the relatives after death.

(2) Those whose relatives were strongly opposed to post-mortems.

Of the 1,000 cases, 454 had massive disease and 546 had simple pneumokoniosis. For the purpose of this study massive pneumokoniosis was deemed to be present if the lung contained a piece of black fibrous tissue more than 3 cm. across.

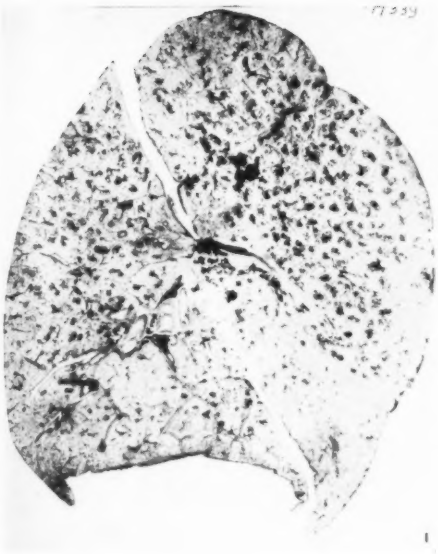
The ages at death of the cases of massive disease are shown in Table I.

TABLE I.—AGE DISTRIBUTION OF 454 CASES OF MASSIVE PNEUMOKONIOSIS

Under 30 yrs.	30 *to* 39	40 *to* 49	50 *to* 59	60 *to* 69	70 *to* 79	80+	*Age not recorded*	*Totals*
0	24	59	137	154	72	2	6	454

It is evident from this table that the condition is compatible with a long life.

Nineteen had worked as trimmers, loading coal into the holds of ships. Seven of these had massive disease. This accords with Gough's (1940) findings and seems to dispose of the theory that the condition is due to highly siliceous dust from rock strata adjacent to the coal seams.



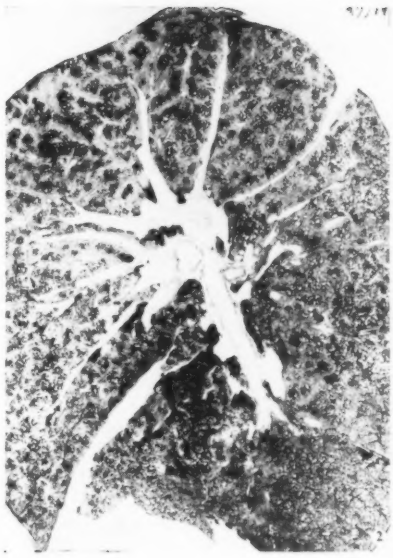
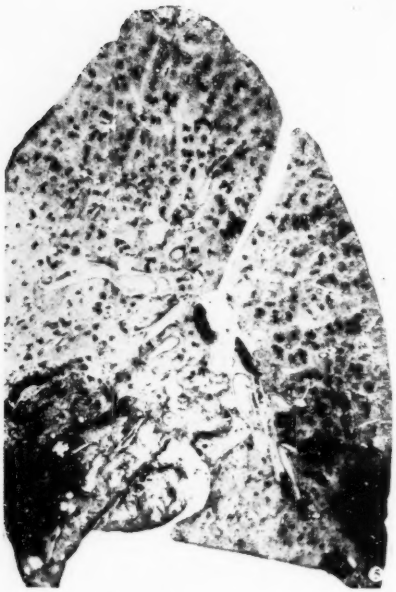


FIG. 1.—A section of the left lung from a coalworker of 65. The right lung contained a massive dust lesion 15 cms. across.

FIG. 2.—The left lung of a coalworker of 63 showing simple pneumokoniosis. The right lung was similar.

FIG. 3.—Massive pneumokoniosis in a coalworker who developed the condition at the age of 25 and died when he was 37. The lesion showed bacteriological evidence of tuberculosis.

FIG. 4.—In this case pneumokoniosis with tuberculosis was diagnosed at the age of 27. He died 3 years later and active tuberculosis was found in the lung lesion at autopsy.



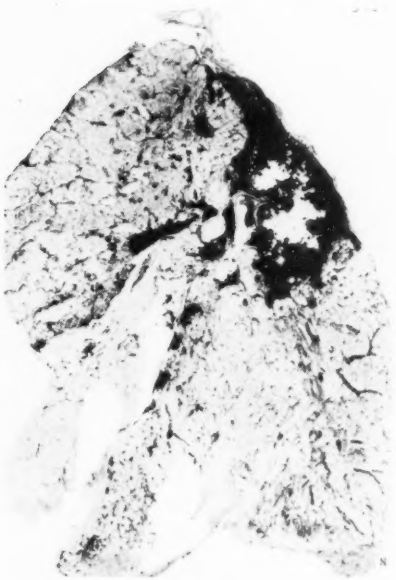


FIG. 5.—Simple pneumokoniosis in a coal-face worker of 35 who died from carcinoma of the stomach. The large dark areas represent infarction.

FIG. 6.—Massive pneumokoniosis in a coal-face worker of 33. He had worked in the same pit for approximately the same time as the miner whose lung is illustrated in Fig. 5.

FIG. 7.—Massive pneumokoniosis in miner age 63. A guinea pig inoculation test of the lesion was negative.

FIG. 8.—Massive pneumokoniosis in a miner age 57. The lesion was positive to guinea pig inoculation.

On examining all the cases of massive disease reasons were found for suspecting that dust alone, even in large quantities, was not the cause. The reasons were as follows:

(1) Simple pneumokoniosis is symmetrical and if massive fibrosis were due to dust alone one would expect each lung to be equally affected. In many cases in this series, however, there was considerable and sometimes gross asymmetry. An example is shown in Fig. 1, which represents the left lung of a patient of 65 who had worked in coal mines since boyhood.

The specimen contained a small cluster of fibrous nodules in the upper lobe near the hilum. The right lung was dissected at autopsy and its upper and middle lobes were entirely destroyed by a massive lesion 15 cm. across.

(2) Reference to Table II shows that 275 cases of simple disease were over 59 years old.

TABLE II.—AGE DISTRIBUTION OF 546 CASES OF SIMPLE PNEUMOKONIOSIS

Under 30	30 *to* 39	40 *to* 49	50 *to* 59	*Over* 59	*Age unknown*	*Totals*
11	22	72	160	275	6	546

In many of the 275 dust accumulation was slight, but in 56 of them there were numerous large dust foci without massive disease. Fig. 2 is an example. It shows the left lung from a man of 63 whose whole working life had been spent in coal mines. Neither lung showed massive fibrosis. The occurrence of such cases as these makes it unlikely that dust alone, even in large amounts and acting over a long period of time, can cause the disease.

(3) Progressive massive fibrosis sometimes occurs in young men with short exposures and with relatively little dust in those parts of the lung which are not fibrosed. Table I records that at death there were 24 under the age of 40. In 11 of these the diagnosis had been made before the age of 30. Two examples are illustrated. Fig. 3 shows a lung from a miner who was found to have massive pneumokoniosis at the age of 25. He died when he was 37 and at autopsy the lesion was found to contain active tuberculosis.

Fig. 4 shows the right lung of a man who at the age of 27 was found to have pneumokoniosis with tuberculosis. He died at the age of 30, and the presence of tuberculosis was confirmed at autopsy.

Examining Table II we note that there were 33 men under the age of 40 who had simple pneumokoniosis only, and the problem is to decide why massive disease was absent in these cases and present in 11 men who were in their twenties. Five of these cases without massive disease appeared to have just as much dust in their lungs as those with massive disease, hence the occurrence of the latter does not appear to depend on the amount of dust present. The localised fibrosis might be due to a special kind of coal dust, but this seems unlikely because all these young miners had worked in the steam coal area and some with massive disease had actually worked in the same mines as those without. Figs. 5 and 6 illustrate this point. Fig. 5 shows a section of the left lung from a miner of 35 who had worked since the age of 15 at the coal face

in a colliery near Porth (Wales). There are numerous dust foci present but no massive disease. The two dark areas in the lower part of the section are due to infarction and bronchopneumonia. The right lung, which was dissected at autopsy, was also free from massive disease. Fig. 6 illustrates a lung from a miner aged 33 who had worked at the coal face in the same pit for approximately the same time. In view of these findings it seems likely that neither the amount of dust, nor the kind of dust, nor the time of action, is the operative factor in producing massive fibrosis

The autopsy material from the 11 who developed the massive disease in their twenties was examined for evidence of tuberculosis. This was found in 9, the criteria being as follows: In 5 there was naked-eye, microscopic and cultural evidence. In 1 further case there was a positive sputum in life, and microscopy showed active tuberculosis. In 3 further cases which were not examined by cultural or inoculation methods, the histology showed active tuberculosis. In the remaining 2 of the 11 the histology was suggestive, but inadequate for a firm diagnosis of tuberculosis.

These examples of the disease occurring in young men show that it can develop after short exposure to dust, and when it does active tuberculosis is often found in the lesion.

At each autopsy one lung was retained intact and expanded with formalin ready for the preparation of a whole lung section by the Gough and Wentworth (1948) technique. The other lung was cut at the time of autopsy. In the whole series massive fibrosis was present in 245 of the lungs cut at post-mortem. The lesion was examined by the naked eye for signs of active tuberculosis, then suspected parts were excised for microscopy, and in 163 cases parts of the lesion were examined by culture and guinea-pig inoculation.

On examining these 245 cases for tuberculosis, 99 cases were found in which there was evidence of its presence. This total was made up as follows:

In 58 cases the diagnosis of tuberculosis was established by obtaining a positive culture or guinea-pig inoculation test from the mass. In a few cases the guinea-pig test was inconclusive and these were recorded as negative.

In a further 17 cases in which cultural or guinea-pig methods were not used there was histological evidence of tuberculosis which was confirmed by detecting the organism in Ziehl-Neelsen preparations of the tissues.

In a further 24 cases in which cultural or guinea-pig tests were not done there was strong histological evidence of tuberculosis, but the organism could not be seen in Ziehl-Neelsen preparations. Each of this latter group showed histological tuberculous follicles or areas of caseation with Langhans giant cells.

Many other cases showed areas of necrosis only or a cytology highly suggestive of tuberculosis, but for the purposes of this paper these were recorded as negative.

On analysing the tuberculosis results by age groups the data shown in Table III were obtained.

Inspection of this table shows that under the age of 40, 15 out of 17 masses were proven tuberculous. With increasing age there is a steady decline in the incidence of tuberculosis findings, until in men over 59 active disease is found in only 29 per cent. of the masses.

These figures might be interpreted as meaning that, in older men, the

TABLE III.—AGE GROUPS

	Under 30 yrs.	30-39	40-49	50-59	*Over 59*	*Age not known*	*Totals*
Tuberculosis positive	0	15 (88%)	22 (51%)	28 (42%)	32 (29%)	2 (33%)	99 (40%)
Tuberculosis negative	0	2 (12%)	21 (49%)	39 (58%)	80 (71%)	6 (67%)	146 (60%)
Totals ..	0	17 (100%)	43 (100%)	67 (100%)	112(100%)	8 (100%)	245(100%)

condition was non-tuberculous. Reasons were found, however, for believing that the initiating factor was likely to be tuberculosis. The reasons were:

(1) Many of the guinea-pig negative cases could be matched by others of similar gross and microscopic appearances from which a positive guinea-pig result had been obtained. An example of such matching is shown in Figs. 7 and 8.

They show the lungs from 2 miners both of whom had over thirty years' exposure to dust. Both were tuberculosis negative to gross and microscopic examination. The lesion of Fig. 7 was negative on guinea-pig inoculation, that in Fig. 8 was positive.

(2) The cytology in the lesions of the older men resembled that in those of the younger ones, which could be shown to be tuberculous in most cases.

(3) The sites of the lesions in the lungs and the relative frequency in sites of predilection is similar to that of chronic tuberculosis.

The evidence for regarding tuberculosis as the essential second factor is not conclusive. In particular, it was disappointing to find that evidence of tuberculosis was present in only one-third of the lesions of older men. Cochrane has shown that in such cases during life positive sputa can be obtained in only 1 per cent. It is interesting to speculate what the result would be if bacteriological tests of serial biopsies were possible from the stage of radiological coalescent mottling to the final stage of massive fibrosis. In those cases which are negative at autopsy it may be that the organisms have died or have been altered in some way which makes their detection specially difficult.

The deductions from the present study have been considered in the light of the experience of the pathologists, clinicians and radiologists mentioned above. On the basis of all the evidence available it is considered probable that the second factor in the etiology of massive pneumokoniosis is tuberculosis.

Summary

Evidence has been given for believing that coal dust alone does not produce massive pneumokoniosis. Additional evidence has been adduced for believing that the condition can occur in the absence of the inhalation of highly siliceous dusts. Results of examinations of massive lesions for tuberculosis have been tabulated and reasons have been given in support of the view that tuberculosis is an essential factor in the etiology of massive pneumokoniosis.

The author acknowledges with thanks the invaluable help given by Dr. Ruth Milne, who undertook the bacteriological work. The material for this investigation was obtained by

Professor J. Gough, who also gave much valuable advice and criticism. Mr. J. E. Wentworth prepared the lung sections and the photography was done by Mr. J. P. Napper.

Fig. 6 was reproduced by kind permission of the editor of the *Journal of the Faculty of Radiologists*.

REFERENCES

AMOR, A. J., and PROSSER EVANS, R. G. (1934): *Practitioner*, 132, p. 700.
BEDFORD, T., and WARNER, C. G. (1943): Spec. Rept. Series, Medical Research Council, No. 244.
BELT, T. H., and FERRIS, A. A. (1942): Spec. Rept. Series, Medical Research Council, No. 243.
COCHRANE, A. L., COX, J. GLYN, and JARMAN, T. F. (1952): *Brit. Med. J.*, **2**, 843.
COX, E. I. (1857): *Brit. Med. J.*, 491.
CUMMINS, S. L., and WEATHERALL, C. (1931): *J. Indust. Hyg. and Tox.*, **31**, 464.
DAVIES, I., FLETCHER, C. M., MANN, K. J., and STEWART, A. (1948): Proc. 9th Int. Cong. on Ind. Med., p. 773.
FLETCHER, C. M. (1948): *Brit. Med. J.*, **1**, 1015.
GARDNER, L. U. (1937): Third Saranac Symposium on Silicosis.
GOODING, C. G. (1946): *Lancet*, **2**, 891.
GOUGH, J., and WENTWORTH, J. E. (1948): Proc. 9th Int. Cong. Ind. Med., London.
GOUGH, J. (1940): *J. Path. and Bact.*, **60**, 277.
HALDANE, J. (1923): "Effects of Dust Inhalation in Miners." Address to South Wales Inst. Engineers.
JONES, J. GLYN (1938): 26th Rept. Welsh Nat. Mem. Ass.
KING, E. J., and NAGELSCHMIDT, G. (1945): Spec. Rept. Series, Medical Research Council, No. 250.
MANN, K. J. (1951): *Thorax*, **6**, 1.
MCVITTIE, J. C. (1949): *Postgrad. Med. J.*, **25**, 290.
MOORE HALL, J. A. (1937): *J. Indust. Hyg. and Tox.*, **19**, 9.
OLIVER, T. (1909): "Allbutt and Rolleston's System," **5**, 462.
POLICARD, A., CROZIER, L., and MARTIN, E. (1939): *Annal. d'Anat. Path.*, **6**, 2.
Pub. Hlth. Bull., U.S. Pub. Health Service (1941): **28**, 270.
ROGERS, E. (1946): *Lancet*, **13**, 1.
SANDER, O. A. (1946): *Journal Lancet*, **66**, 4.
SEN, P. K. (1937): *J. Indust. Hyg. and Tox.*, **19**, 6.
STEWART, A. (1948): *Brit. J. Indust. Med.*, **5**, 120.
WILLIAMS, E. (1933): "The Health of Old and Retired Miners in South Wales." Univ. of Wales Press Board.

PREGNANCY AND PULMONARY TUBERCULOSIS

By J. B. Cromie*

From the Northern Ireland Tuberculosis Authority

In recent decades medical opinion regarding the effect of pregnancy on pulmonary tuberculosis has varied widely. Hippocrates is credited with the statement that pregnancy had a beneficial effect on pulmonary tuberculosis, and his authority was such that physicians and obstetricians held firmly to this belief for several centuries. In the late nineteenth century opinion reverted sharply and pregnancy in the tuberculous female was then regarded as a disaster to be countered with immediate therapeutic abortion—an attitude neatly expressed as follows: " for the virgin, no marriage; for the married, no pregnancy; for the pregnant, no confinement; for the mother, no suckling." In more recent years the publications of several authors (Cohen, 1946; Freedman and Garber, 1946; Stewart and Simmonds, 1947; Turner, 1950; Edge, 1952; Cohen *et al.*, 1952) have brought the pendulum of medical opinion to a more neutral point where it is considered that pregnancy *per se* has little or no effect on the ultimate medical history of a tuberculous female.

In the present series of cases the data are collected from the hospital and clinic records of tuberculous females in whom one or more pregnancies have occurred. Many such records were examined, but owing to inadequate information 101 pregnancies occurring in 72 mothers were finally chosen as suitable for analysis. In order to gain as accurate an idea as possible of the effect of pregnancy and the puerperium on tuberculosis, only those cases in whom a diagnosis of tuberculosis had been made before conception or during the early months of pregnancy are considered.

All the patients were followed up for six months after delivery. Deterioration of the tuberculous lesion after this time, although it may be due to the late effects of pregnancy and the puerperium, depends also on several other factors.

Any radiological or bacteriological evidence of retrogression, however slight, which occurred during the period of observation was accepted as due to pregnancy and puerperium.

Of the 101 cases the tuberculous disease was considered to be active in 45 cases and inactive in 56 cases at the time of conception or diagnosis. The tuberculous lesions remained unchanged throughout the period of observation in 51 cases, improvement took place in 14 cases and deterioration in 31 cases. In 5 of these 31 cases death from tuberculosis took place within the period of observation, and all 5 had had active disease at the time of conception.

Of the 31 cases who deteriorated—deterioration took place in the first trimester of pregnancy in 13 cases, in the second trimester in 3 cases, in the third trimester in no cases, in the first three months of the puerperium in 14 cases and in the second three months of the puerperium in 6 cases. In

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some cases deterioration took place at more than one of the above-named periods.

The 14 cases who improved all had originally active disease and all had hospital treatment. No case had a therapeutic abortion.

Status of disease at time of conception or diagnosis	*Unchanged*	*Improved*	*Worse*	*Death in 1st 6/12 of puerperium*
Active 45	9	14	17	5
Inactive 56	42	—	14	—

TIMES OF DETERIORATION IN 31 CASES

Pregnancy			*Puerperium*	
1st 3/12	2nd 3/12	3rd 3/12	1st 3/12	2nd 3/12
13	3	—	14	6

From these figures the following tentative conclusions may be drawn:

(*a*) That approximately half the mothers with active pulmonary tuberculosis will suffer an extension of their disease in association with pregnancy and the puerperium.

(*b*) That approximately one-quarter of the mothers with inactive pulmonary tuberculosis will suffer an extension of their disease in similar circumstances.

(*c*) That if extension does occur it is most likely to do so in the first three months of pregnancy and/or in the first three months of the puerperium.

REVIEW OF RECENT LITERATURE

A brief review of the literature regarding the effect of pregnancy on pulmonary tuberculosis shows a marked change in opinion. Prior to 1930 most observers considered that pregnancy had an unfavourable effect on pulmonary tuberculosis, while the majority after that date were unanimous in stating that pregnancy had little or no effect on the long-term history of the tuberculous disease.

Reference to the experimental work of Burke (1940), who studied pulmonary lesions in rabbits after intrathecal injection of human and bovine organisms, showed that no difference could be detected in the pathological findings in pregnant and in non-pregnant female rabbits nor in male rabbits similarly injected.

Roe (1946) and Jacobs (1946), as a result of radiographic surveys, have shown that the incidence of pulmonary tuberculosis is no greater in pregnant females than in others of the same age group. Jameson (1938) found that the death rate from tuberculosis was no greater in multiparous than in nulliparous females in whom the lesions were of similar extent and who were in the same age group. Stewart and Simmonds (1947), in a survey of pregnant females with active and with inactive disease and of non-pregnant controls, concluded

that " pregnancy as an event in the course of a tuberculous illness has little or no effect upon the progress of pulmonary disease over a period of fifteen months whether the disease be active or quiescent; deterioration in the state of some tuberculous patients must be expected whether they are pregnant or not." They further noted that " patients whose pregnancy was terminated proved no better than those going to term or the control patients who had no pregnancies related to the period of observation." Similarly Edge (1952) could find no evidence that " pregnancy whether terminated or allowed to continue had any effect on the course of the disease " and could find " no indication for therapeutic abortion as the outcome seemed to be similar whether the pregnancy is terminated or not." Turner (1950) stated that " if the course of the disease is in some cases influenced unfavourably, this is more than counterbalanced by the cases in which pregnancy influences the course of the disease favourably."

Cohen *et al.* (1952) in a study extending over five to twenty years, comprising 149 mothers with 401 full-term pregnancies, could " incriminate neither the child-bearing incident nor other specific factors relating to pregnancy as potentially dangerous for tuberculosis. The anatomic extent of the disease, the pathological pattern and the native resistance or susceptibility of the individual patient to tuberculosis appear from the study to be the essential factors which determine the course and prognosis of the tuberculous mother." In a long review of recent literature Freedman and Garber (1946) concluded " that pregnancy exerts little or no influence on the incidence or course of pulmonary tuberculosis and that therapeutic abortions should never be performed after the first trimester and very rarely, if at all, during the earlier months of gestation."

Times of Deterioration and Possible Causes

Reference to the present series shows that deterioration is most likely to take place in early pregnancy or in the early puerperium or both. Turner (1950) showed that of 115 cases diagnosed during pregnancy 68 were diagnosed in the first trimester, and of 122 cases diagnosed in the year after pregnancy 71 were diagnosed in the first three months of the puerperium. It must, therefore, be accepted that these are " danger periods " when the tuberculous lesion is most likely to extend.

When searching for possible causes of progression of disease, several suggestions were noted in the literature—*p*H changes, calcium depletion, hypercholesterolæmia, low calorie intake and/or hyperemesis, altered skin sensitivity to tuberculin, altered capillary permeability, and the possible action on fibrous tissue of the proteolytic ferments responsible for involution of the uterus.

Endocrinological Changes

Browne *et al.* (1939) estimated the blood levels of œstrogen and chorionic gonadotropin during pregnancy and showed that there is a sharp rise in the gonadotropin level in early pregnancy which then falls to an approximately normal level throughout the remainder of pregnancy and the puerperium. The œstrogen level is normal during early pregnancy, rises in the late months and then falls abruptly at term. Lurie *et al.* (1949) working with rabbits showed

that œstrogens retarded the tuberculous process at the site of inoculation into the skin, while gonadotropin uniformly enhanced the tuberculous process at the site of inoculation. This work suggests that deterioration in early pregnancy may, at least in part, be due to the high level of circulating gonadotropin while the deterioration in the puerperium may be due to the sudden withdrawal of the " protective " œstrogen. The increased excretion of cortical hormones from the adrenal glands physiologically hypertrophied during pregnancy may be a factor causing deterioration, and changes in tuberculin sensitivity induced by these hormones also have a hypothetical bearing on the mechanism of deterioration.

Changes in Diaphragmatic Level

It would seem reasonable to suppose that the diaphragm is displaced upwards into the thorax by the enlarging uterus late in pregnancy and that the subsequent abrupt descent on delivery might be responsible for the puerperal deterioration. To check this assumption, note was made of the diaphragmatic level relative to the posterior ends of the ribs in inspiratory chest films of pregnant females taken in the last weeks of pregnancy before " lightening " had occurred and again after delivery. The difference in diaphragmatic levels averaged 0·75 inch with a range of 0-2 inches. As a control similar measurements were made on inspiratory films of non-pregnant females, when an average difference of 0·4 inch was found. As a general rule, therefore, the diaphragm undergoes only slight alteration in level during pregnancy. Stewart (1951) and Cohen (1946) similarly found that the change in diaphragmatic level was small, and the latter also noted " that it was never necessary to give a pneumothorax refill immediately after delivery to compensate for the alleged fall in intrapleural pressure thought to occur as a result of descent of the diaphragm." Cugell *et al.* (1952) noted in their spirometric studies that " the changes in lung volumes with pregnancy in normal women were often so small that they were considered within the normal limits of variation . . . A small and somewhat variable degree of collapse is afforded by pregnancy at full term . . . It is unlikely that all improvement in pulmonary tuberculosis during pregnancy is due to collapse afforded by elevation of the diaphragm."

It would appear, therefore, that the induction of pneumoperitoneum immediately after delivery is a measure of no practical value despite the somewhat unconvincing evidence of Dingle (1944), who claimed to have prevented breakdown in 27 out of 30 patients by such induction. Cohen *et al.* (1952) have, however, induced a pneumoperitoneum three to four days after delivery for " exudative and cavity disease in the lower two-thirds of the lung—a site unsuited for other forms of collapse therapy."

Advice to Patient

Although no controls are available for the present series of cases it would appear from the results that the following advice should be given to female patients: (*a*) Those with inactive disease may embark on a pregnancy with relative safety. The longer the disease is in an inactive state and the less extensive the lesions, the better the prognosis. (*b*) Those with active disease should

be discouraged from pregnancy until every effort has been made, using all available means, to bring the disease under control and until the disease has been inactive for two to three years. If active tuberculosis is diagnosed during pregnancy it should be treated exactly as the same lesion in a non-pregnant person. With present-day effective therapy there are apparently no indications for therapeutic abortion.

Summary and Conclusions

The frequency of progression of tuberculosis during pregnancy and puerperium has been indicated for active and inactive disease. The common use of the term " danger periods " for the early months of pregnancy and the puerperium when deterioration is liable to occur is a little difficult to reconcile with the statements that pregnancy has little or no effect on the course of pulmonary tuberculosis. Possible causes for deterioration at these times are discussed. The frequency of extension of tuberculosis in this series is higher than most in the literature. A danger of extension does exist and should not be ignored or minimised as seems to be the modern tendency.

All the patients in this survey were under the care of the various physicians of the Northern Ireland Tuberculosis Authority, to whom I wish to express my thanks for permission to review the notes and X-rays.

REFERENCES

Brown *et al.* (1939): *Amer. J. Obst. and Gynæc.*, **38**, 927.
Burke, H. E. (1940): *Surgery, Gynæc. and Obstetrics*, **71**, 615.
Cohen, R. C. (1946): *Brit. J. Tuber. and Dis. Chest*, **40**, 10.
Cohen *et al.* (1952): *Amer. Rev. Tuber.*, **65**, 1.
Cugell *et al.* (1952): *Trans. N.T.A.*, 142.
Dingle, P. (1944): *J. Obs. and Gynæc.*, **51**, 499.
Edge, J. R. (1952): *Brit. Med. J.*, **1**, 845.
Friedman and Garber (1946): *Amer. Rev. Tuberc.*, **54**, 275.
Jacobs, A. L. (1946): *J. Obst. and Gynæc.*, **53**, 368.
Jameson, E. M. (1938): *Amer. J. Obst. and Gynæc.*, **36**, 59.
Lurie *et al.* (1949): *Amer. J. Tuberc.*, **59**, 168, 186.
Roe, J. T. N. (1946): *Tubercle*, **27**, 51.
Stewart, C. J. (1951): *Tubercle*, **32**, 40.
Stewart *et al.* (1947): *Brit. Med. J.*, **2**, 726.
Turner, H. M. (1950): *Lancet*, **1**, 697.

TOXIC REACTIONS TO PARA-AMINO-SALICYLIC ACID

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Para-amino-salicylic acid (P.A.S.) was introduced in 1946 by Lehmann. Since 1948 it has been widely used in the treatment of pulmonary tuberculosis. In 1949 Graessle and Pietrowski discovered that P.A.S. prevented or delayed the emergence of streptomycin-resistant strains of tubercle bacilli *in vitro*. This finding has since been amply confirmed in a clinical trial by the Medical Research Council (1950), in which it was shown that streptomycin-resistant strains only rarely appear when P.A.S. is also given. The most recent report of the Medical Research Council's Tuberculosis Chemotherapy Trials Committee (1953d) has indicated that P.A.S. and isoniazid " make a very effective combination of drugs." Over a period of three months P.A.S. was able to prevent the emergence of isoniazid-resistant tubercle bacilli.

It is probable that P.A.S. will continue to play an important part in the treatment of tuberculosis. Now that an effective combination of drugs, both of which can be taken by mouth, is available it is possible that P.A.S. and isoniazid may be used in the treatment of ambulant patients in the older age groups as well as in younger patients resting in bed at home. It is, therefore, of increasing importance to recognise the serious toxic effects which P.A.S. may occasionally produce.

These toxic effects may be divided into three broad groups. Firstly, there is the direct irritant action of the drug upon the gastro-intestinal mucous membrane. Nausea was reported in up to 50 per cent. of cases by Nagley and Logg (1949) and Madigan *et al.* (1950), and anorexia of some degree is even more common. Diarrhœa and vomiting occurred in 22 of Madigan's 64 patients and in about 30 per. cent. of the cases in the Medical Research Council trial (1950). The effects are related to dosage, to the preparation used and to the times of administration. Russell (1952) has shown that calcium P.A.S. may sometimes be taken without incident when the sodium salt has not been tolerated.

Secondly, P.A.S. sometimes produces pharmacological side-effects. Thyroid enlargement has been described by Davies *et al.* (1953) and Hamilton (1953). Komkrower (1951) reported a case of thyroid enlargement and myxœdema in a girl aged 8½ years.

Hypokalæmia, causing cardiac irregularities and transient paralyses, was first described by Cayley (1950), and Heard *et al.* (1950) reported 12 cases from Australia. Allen *et al.* (1953) described a fatal case of hypokalæmia in which jaundice also occurred. Although both these reactions were due to P.A.S., for reasons that will appear later they do not seem to have been caused by the same mechanism. Strong (1951) considered that liquorice extract used in

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flavouring caused the fall in blood potassium by a deoxycortone-like action, but Jones and Leggat (1953) report a case of hypokalæmia due to P.A.S. in which no liquorice was given.

The third main group of toxic effects is the most severe. These are the hypersensitivity reactions, and they vary in intensity from transient pyrexia to a serious illness often associated with hepatitis. Fever, sometimes accompanied by other manifestations of hypersensitivity but often alone, may occur from the second to the sixth week of P.A.S. therapy. Pyrexia of sudden onset in a patient receiving P.A.S. should always be regarded as a drug fever and antibacterial treatment stopped until a definite diagnosis is made.

Skin rashes of erythematous, morbilliform or urticarial type, usually irritating and sometimes followed by desquamation or more rarely by exfoliative dermatitis, are not infrequent. Kierland and Carr (1949) estimated that rashes occurred in 2-4 per cent. of patients; 7 of 112 patients in the Medical Research Council Trials (1950) developed rashes. Yeh (1952) observed only three rashes (0·5 per cent.) in 590 patients receiving P.A.S. Five of 165 patients receiving P.A.S. in Medical Research Council Trials of Isoniazid (1952) and 2 of 102 in the Second Medical Research Council Trials (1953a) had severe toxic reactions, but the type of reaction is not stated. Three of 203 (1·5 per cent.) patients in the most recent chemotherapy trial had to be excluded because of skin reactions to P.A.S. (Medical Research Council 1953d). Hayes and Weiss (1953) report serious hypersensitivity reactions occurring in 4 per cent. of 255 patients, and Warring and Howlett (1952) give an incidence of 2·5 per cent. of 275 patients.

Asthma has been described by Gerrits (1951) in 2 cases following P.A.S. administration for four weeks. Transient pulmonary infiltrations similar to those described by Löeffler occurred in one case described by Warring and Howlett (1952) and the relationship to P.A.S. administration is convincing. Other symptoms attributed to P.A.S. hypersensitivity include coryza, headache (which is quite common), angioneurotic œdema, laryngeal stridor, spasmodic cough, blood dyscrasias, lacrimation and conjunctivitis. Some of these symptoms are transient and many do not interfere with treatment.

Hepatitis, which is probably the most serious toxic effect of P.A.S., was first described in 1950 by Cuthbert (1950) and independently by Hurrell (1950). These papers were followed by a series of reports describing similar cases (Livingstone and Street, 1950; Scott and McCann, 1950; Hess and Ismay, 1950; and Landsborough, 1951). Since then occasional cases have been recorded in the literature, but the incidence is difficult to estimate. Lichtenstein and Cannemeyer (1953), reviewing 8 cases of severe hypersensitivity to P.A.S. among approximately 3,000 patients, describe 1 case of jaundice and 2 other cases in which the serum bilirubin was raised and liver function tests were abnormal, but in whom jaundice was not obvious clinically. In addition to cases of jaundice other evidence of interference with liver function has been given by Madigan *et al.* (1950), Nagley (1949) and Kristenson (1953). These authors showed that the prothrombin time was increased during P.A.S. therapy and it was considered that this was caused by impairment of prothrombin production in the liver. Swanson (1949) reported hypoprothrombinæmia in 5 of 6 cases of rheumatoid arthritis treated by P.A.S. Lynch (1950), however,

considered that the increase in prothrombin times which he observed was without clinical significance. Julian (1952) describes pyrexia and a rash occurring in a patient receiving streptomycin and P.A.S., and, although jaundice did not appear, liver function tests were abnormal.

The following case presents no features which have not already been described. It is considered justifiable again to draw attention to an unusual manifestation of hypersensitivity to P.A.S. in view of the increasing use of this drug.

Case Report

A married woman, aged 33, began to feel ill in March 1953, and in August she developed a cough. A chest radiograph on August 29, 1953, showed extensive pulmonary tuberculosis with a large tension cavity in the left upper lobe. Tubercle bacilli were present in the sputum. She remained in bed at home and on September 10 streptomycin 1 G. daily with P.A.S. 18 G. daily was commenced.

On September 15 she was admitted to hospital. On admission she was a very ill woman. Temperature was normal and the radiographic appearances were unchanged. Streptomycin was continued with P.A.S. 16 G. daily and isoniazid 200 mgm. daily was added. There was no history of allergy. She had had an attack of jaundice, presumably caused by virus hepatitis, at the age of 7 years.

Progress was uneventful until—

Oct. 5. The evening temperature was 101·2° F. and she complained of a superficial inflammation of the buttock.

White cell count: Total 5,200 cells per c.mm.

Neutrophils ..	75 per cent.	Lymphocytes ..	14 per cent.
Eosinophils ..	5 „ „	Monocytes ..	6 „ „

This infection was cleared by the addition of penicillin to her treatment, and temperature returned to normal.

Oct. 7. The patient complained of an irritation on the skin of the legs. No rash could be found despite careful search, but promethazine 50 mgm. twice daily was given to relieve the itching.

Oct. 9. Streptomycin was stopped. She had had 30 G. streptomycin, and it has been our practice to change from daily to intermittent streptomycin at this point. P.A.S. 16 G. and isoniazid 200 mgm. daily were continued.

Oct. 13. She returned home at her own request to settle domestic difficulties. She had then received a total of 31 G. streptomycin, 5·6 G. isoniazid and 538 G. P.A.S. On her arrival home she was taken ill and had a rigor; her temperature rose to 105° F. and she vomited repeatedly and could take no more P.A.S. She had no diarrhœa and although the skin still irritated a little she had no rash.

Oct. 14. The morning temperature was 103° F. She was given an injection of penicillin 1 mega unit and aureomycin 0·5 G. six-hourly.

Oct. 15. Pyrexia continued and a generalised erythematous rash appeared. Penicillin was stopped.

Oct. 16. Streptomycin 1 G. intramuscularly was given as requested on her discharge from hospital. She was by now extremely ill and somewhat shocked. The urine was small in amount and very dark in colour. She was visited at home by the Chest Physician and in consequence was readmitted to hospital at 2·25 p.m.

On admission temperature was 104° F., the patient was in poor general condition, but no abnormal physical signs were found except the rash and those signs which had previously been found in the chest. Blood pressure was 115/75. Blood cultures were taken (these were later to prove negative).

White cell count: Total 13,200 cells per c.mm.

Neutrophils	79 per cent.	Lymphocytes	18 per cent.
Eosinophils	1 „ „	Monocytes	2 „ „

A diagnosis of severe hypersensitivity to P.A.S. was made and promethazine 50 mgm. twice daily was given.

Oct. 17. Her general condition had deteriorated; she was not fully conscious, her blood pressure had fallen to 85/60, and for the first time an icteric tinge was noted in the conjunctivæ. The spleen was palpable, but there was so much guarding over the tender liver that it could not be felt. The rash was unchanged. Bile pigments were present in the urine. Streptomycin 1 G. and isoniazid 200 mgm. daily were recommenced.

Oct. 19. Jaundice was now obvious, the spleen was still palpable but smaller. There was some œdema of the face.

Serum bilirubin	7·2 mgm. per 100 ml.
Van den Bergh reaction	Positive direct
Thymol turbidity	6 units
Serum sodium	137·3 mEq/litre
Serum potassium	4·23 mEq/litre
Serum proteins	5·0 G. per cent.
Albumin	2·9 G. „ „
Globulin	2·1 G. „ „
A/G ratio	1·41

The general condition had improved and she could now take a high protein diet. From that time onwards she made a slow but continuous improvement.

Oct. 22. The spleen was no longer palpable.

White cell count: Total 8,600 cells per c.mm.

Neutrophils	62 per cent.	Lymphocytes	5 per cent.
Eosinophils	32 „ „	Monocytes	1 „ „

Direct eosinophil count 2,700 per c.mm.

Oct. 23. The temperature returned to normal but the jaundice deepened.

Serum bilirubin 14·4 mgm. per cent.

Oct. 28. The jaundice had become less marked.

Serum bilirubin 7·0 mgm. per cent.

Streptomycin (total 42 G.) and isoniazid (total 7·8 G.) were discontinued. The patient was out of immediate danger and it was considered wise to stop these drugs lest hypersensitivity might develop to them.

Nov. 5. Direct eosinophil count 450 per c.mm.

Prothrombin time	Normal
Skin patch tests with 10 per cent. P.A.S. solution	Negative

Nov. 16. Despite repeated warnings against such a course the patient discharged herself against medical advice.

On discharge she was still faintly jaundiced but her general condition was much improved. The chest radiograph showed no change in the infiltration and cavitation first observed. No deterioration had occurred but the response to chemotherapy was poor.

The diagnosis of hypersensitivity to P.A.S. seems fairly certain in this case despite the negative skin test.

Hæmolytic jaundice is unlikely as bile pigments were present in the urine. Liver function tests suggested parenchymal damage.

There was no history of contact with a case of infective hepatitis and no case occurred in the ward in the preceding twelve or the following four months. No case of syringe-transmitted jaundice has occurred recently in the hospital. The clinical picture was not that of virus hepatitis and the blood picture showed a leucocytosis. In virus hepatitis there is usually a leucopænia or a normal white cell count, according to Whitby and Britton (1950).

Leptospirosis is a possible diagnosis, but there was no albuminuria. Unfortunately agglutination reactions were not carried out. There was no history of contact with rats; the patient had been in hospital for three weeks prior to the onset of jaundice, the incubation period of Weil's disease being six to twelve days.

No other drug with known hepatotoxic effects was given. As far as can be determined no case of hepatitis definitely proved to be due to streptomycin has been reported.

Streptomycin and isoniazid were recommenced at the height of the jaundice, which diminished while they were given. It seems, therefore, unlikely that either of these drugs was the responsible agent. The presence of pre-existing liver damage consequent upon the childhood jaundice cannot be ignored, but it is unlikely that this affected the reaction to P.A.S.

While every attempt has been made to exclude an intercurrent cause for the jaundice, it is felt that toxic hepatitis due to P.A.S. should now be recognised by its characteristic clinical features. In support of this hypothesis details of 25 other cases of jaundice in patients receiving P.A.S. which have been described in the literature are set out in the table.

Brun *et al.* (1951) discuss the ætiology of 15 cases of jaundice in patients receiving P.A.S. during the course of eighteen months. With one or two possible exceptions the evidence for incriminating P.A.S. is not strong and few details are given. In addition to the case he describes, J. H. Thomas (1952) mentions four unpublished cases. In the case described by Lichtenstein and Cannemeyer (1953) previously mentioned few details are given and it is, therefore, not included. Brooke and Cable (1952) describe jaundice in a patient receiving P.A.S. in addition to the case (No. 14) included in the table, but again few details are given.

Gow (1951) reported two cases of jaundice occurring at the start of a second course of P.A.S., the first course having lasted one month. No rash occurred, there was no eosinophilia, and they have both since been desensitised to P.A.S. (Gow, 1954). P.A.S. seems to have been the causal agent in these cases, but they do not present the same clinical picture as the majority of cases described, and it is possible that the mechanism was not the same.

Several conclusions can be drawn from a study of this table.

1. Jaundice occurs twenty-two to forty-six days after the start of P.A.S. therapy. McKechnie's case (No. 18) is an exception, jaundice occurring very much later, after sixty-four days.

2. The dosage necessary to produce jaundice varies from 163 G. to 820 G.,

TABLE 1.—DETAILS OF 26 CASES OF JAUNDICE IN PATIENTS RECEIVING P.A.S. WHICH HAVE BEEN REPORTED IN THE LITERATURE

No.	Authority	Day of P.A.S. Therapy on which symptom occurred			Total Dosage of P.A.S. (in Gms.)	Total White Cell Count per c.mm.	Eosinophilia %	Associated Symptoms
		Pyrexia	Rash	Jaundice				
1	Hurrell	?	19	22	163	—	—	Œdema of the face, vomiting, retention of urine.
2	Cuthbert	30	39	41	820	18,600	17	Lymphadenopathy, anuria (13 hrs) exfoliative dermatitis.
3	Livingstone and Street	26	28	28	560	24,000	30	Œdema of ankles, anuria (36 hrs), uræmia.
4	Scott and McCann	22	22	28	440	8,600	9	Lymphadenopathy.
5	Hess and Ismay	27	27	39	324	7,000	11	None.
6	Landsborough	27	29	34	465	32,000	—	Dehydration. *Death.*
7	McKendrick	23	26	35	576	23,125	6	Lymphadenopathy, severe exfoliative dermatitis.
8	Fullerton *et al.*	37	37	42	424	14,200	17	Lymphadenopathy, splenomegaly.
9	Thomas—initial attack	26	27	40	471	16,200	21	Arthritis.
	—recurrence 10 months later	3	3	10	180	—	—	
10	Heard *et al.*	27	29	33	435	—	—	Hypokalæmia.
11	Grandjean	31	31	40	420	13,600	20	Exfoliative dermatitis.
12	McManis and Mira	33	38	41	504	17,950	17	"
13	Jeffery *et al.*	27	28	40	504	70,000	19	Lymphadenopathy, renal damage, stomatitis, exfoliative dermatitis.
14	Brooke and Cable	27	30	34	540	Leucocytosis	23	Œdema of face, albuminuria.
15	Steel	21	27	40	450	14,300	15	Lymphadenopathy, exfoliative dermatitis.
16	Ferguson *et al.*	28	36	46	540	12,500	0	Œdema of face, albuminuria.
17	Rowlands	23	23	29	345	Leucocytosis	—	Exfoliative dermatitis, stomatitis.
18	McKechnie	47	48	64	560	27,000	31	Asthma, lymphadenopathy, exfoliative dermatitis, stomatitis.
19	Mann	24	24	36	246	27,500	33	Arthritis, anuria (19 hrs).
20	Allen *et al.*	27	31	42	372	10,400	—	Hypokalæmia. *Death.*
21	Cuthbert, Case 1	26	26	29	312	8,800	8	Lymphadenopathy.
22	" Case 2	28	28	33	336	Not stated	3	"
23	Muri	34	41	43	700	5,300	0	Agranulocytosis. *Death.*
24	Hayes and Weiss 1	31	42	44	372	10,150	7	Lymphadenopathy, œdema of face.
25	" " " 2	33	?	?	396	Not stated	*	Lymphadenopathy.
26	This case	32	35	37	538	13,200	18	Œdema of face, splenomegaly.

* Absolute eosinophil count=700 per c.mm.

and 180 G. was necessary to produce a recurrence in Thomas's case (No. 9). Time and dosage are so closely related that it is impossible to discover which is the more important factor.

3. Jaundice is preceded by pyrexia which is of sudden onset, and a rash.

4. Excluding the case described by Livingstone and Street (No. 3), in which rash and jaundice occurred simultaneously, a period of from two to sixteen days elapsed between the rash and the appearance of icterus. It would seem unwise, therefore, to start desensitisation until at least a month after the last signs of hypersensitivity have disappeared.

5. Eosinophilia was found in 18 of 21 cases in whom the blood was examined. Of the other 5 cases, 2 had no blood count performed and 3 had a total white cell count which was raised, but no differential count was recorded.

The finding of eosinophilia is of diagnostic importance as it is rare in other forms of jaundice. Its absence, however, does not exclude a hypersensitivity reaction. It should be noted that eosinophilia may be transient and appear late. Serial blood counts are often necessary to discover the eosinophilia.

6. Other manifestations of hypersensitivity are nearly always present, and indeed jaundice may be regarded as one facet of a complex allergic reaction. Anuria is sometimes described but usually lasts only a few hours. Lymphadenopathy, angioneurotic œdema, splenomegaly, joint pains, glossitis and stomatitis are the most frequently associated symptoms. Exfoliative dermatitis is a grave complication.

Sixteen cases out of the 26 were given streptomycin with P.A.S. The reactions do not seem to have been influenced by streptomycin.

The characteristic clinical picture of toxic hepatitis due to P.A.S. has a sudden onset with pyrexia, accompanied by, or followed two to ten days later by, a rash. A few days after the rash jaundice appears. Associated symptoms of hypersensitivity of varying degree are almost always present. Eosinophilia is a useful diagnostic finding.

Liver function tests indicate more or less extensive liver damage, but are of less value in diagnosis than consideration of the clinical features. Skin testing by the usual method of applying a piece of gauze soaked in P.A.S. solution to the skin of the thigh was carried out in many cases, but the results are variable. Hayes and Weiss (1953) state that patch tests are not helpful in establishing a diagnosis, and this contention is supported in the cases reviewed —*i.e.*, only 9 of 14 tested were positive.

Steel (1952) used a method which gave better results and this is described in detail by Hill (1953).

The mortality is at first sight high, 3 cases out of 26 having died, but in the case described by Allen *et al.* (No. 20) hypokalæmia was also present, and in Landsborough's case (No. 6) dehydration may have been a factor.

In that described by Muri (No. 25) agranulocytosis was co-existent. Cuthbert (1953) mentions a fatal case of hepatitis due to P.A.S. reported to him by W. F. Tyrrell in a personal communication, but this is the only case reported in which death occurred from hepatitis *per se*.

Post-mortem examination was performed in 2 cases and the presence of extensive parenchymal liver damage was confirmed. No specific pathology was discovered. Liver biopsy has not been described in cases of hypersensitivity to P.A.S., but this investigation might be well worth while performing, even in cases in whom jaundice is not obvious.

Treatment of the condition is immediately to withdraw the offending drug, and this should be done at the first sign of hypersensitivity. It may be justifiable in some cases to continue with other antibiotics, but in general this should be avoided lest hypersensitivity develop to them. It is important to assure that the patient is given no other salicylates.

From a study of the case reports it was noted that P.A.S. was continued after the occurrence of a rash in only 5 of 25 cases. In case No. 25 insufficient

evidence is given to show when P.A.S. therapy was stopped. This finding seems to disagree with the suggestion made by McKendrick (1951) that jaundice is likely to occur only if P.A.S. is continued in the presence of a rash.

P.A.S. was, however, continued after the first sign of hypersensitivity in 17 of the 25 cases, and it would appear that the more severe reactions occurred when P.A.S. was continued in the presence of allergic symptoms. The mild attacks of jaundice were most common in patients in whom P.A.S. was stopped at the first sign of a reaction. This correlation is not absolute, but it is clear that P.A.S. therapy should be stopped in a patient who shows any evidence of hypersensitivity. Antihistamines may be helpful in relieving symptoms, but they seem to have little effect on the progress of the hepatitis.

On general principles the patient should be given extra fluids and a high protein diet, provided renal function is unimpaired. These patients are often very ill and it is advisable to admit to hospital anyone exhibiting the early manifestations of hypersensitivity.

Recovery has apparently been complete in most of the cases described, but no long-term follow-up of hepatic function has been carried out. Desensitisation to P.A.S. is usually possible without great difficulty by the method described by Horne (1949) and by Climie (1950), and recently elaborated by Crofton (1953b) and by Hayes and Weiss (1953).

Several cases of P.A.S. hepatitis have, after desensitisation, been able to continue therapy for long periods without incident. The case described by Thomas (1952) illustrates the importance of achieving desensitisation before P.A.S. is restarted. In this case jaundice recurred some months later when P.A.S. was given in another hospital.

Summary

The literature of toxic reactions to P.A.S. is briefly reviewed.

A case of toxic hepatitis due to P.A.S. is described.

The clinical picture of this hypersensitivity reaction is discussed with reference to 25 other cases described in the literature.

It is concluded that the triad of pyrexia of sudden onset, rash and jaundice occurring during the exhibition of P.A.S. is characteristic of hepatitis due to the drug. Eosinophilia is a useful diagnostic finding.

Desensitisation to P.A.S. has been successfully performed in a number of cases.

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REFERENCES

Allen, H. S., Beacham, E. G., and Keschner, H. W. (1953): *Amer. Rev. Tuberc.*, **68**, 136.
Brooke, N. H., and Cable, J. V. (1952): *N.Z. Med. J.*, **51**, 368.
Brun, J., Viallier, J., and Kalb et Riffat, J. -C. (1951): *Lyon Med.*, **185**, 349.
Cayley, F. E. de W. (1950): *Lancet*, **1**, 447.
Climie, H. (1950): *Lancet*, **2**, 308.
Crofton, J. W. (1953b): *Brit. Med. J.*, **2**, 1014.
Cuthbert, J. (1950): *Lancet*, **2**, 209.
Cuthbert, J. (1953): *Glasg. Med. J.*, N.S. **34**, 52.
Davies, T. W., Morgan, D. B., and Thomas, J. H. (1953): *Brit. J. Tuberc.*, **47**, 233.
Fergusson, A. G., McIntyre, J. P., and Gemmell, A. R. (1952): *Brit. Med. J.*, **1**, 855.

FULLERTON, J. M., HADEN, P. J., and PRITCHARD, E. K. (1951): *Lancet*, **2**, 941.
GERRITS, J. C. (1951): *Geneesk. Gids.*, **29**, 169.
GOW, J. G. (1951): *Lancet*, **2**, 941.
GOW, J. G. (1954): Personal communication.
GRAESSLE, O. E., and PIETROWSKI, J. J. (1949): *J. Bact.*, **57**, 459.
GRANDJEAN, L. C. (1951): *Ugeskr. Laeg.*, **113**, 83.
HAMILTON, R. R. (1953): *Brit. Med. J.*, **1**, 29.
HAYES, R. H., and WEISS, M. (1953): *Dis. Chest*, **23**, 645.
HEARD, K. H., CAMPBELL, A. H., and HURLEY, J. J. (1950): *Med. J. Aust.*, **2**, 606.
HESS, E., and ISMAY, D. G. (1950): *Lancet*, **2**, 456.
HILL, A. B. (1952): *Brit. Med. J.*, **2**, 938.
HORNE, N. W. (1949): *Lancet*, **2**, 348.
HURRELL, G. (1950): *Brit. Med. J.*, **2**, 729.
JEFFERY, B., BORRIE, P., and MACDONALD, N. (1952): *Brit. Med. J.*, **2**, 647.
JONES, G., PENRHYN, and LEGGAT, P. O. (1953): *Tubercle*, **34**, 112.
JULIAN, D. G. (1952): *Brit. Med. J.*, **2**, 476.
KIERLAND, R. R., and CARR, D. T. (1949): *Proc. Mayo Clin.*, **24**, 539.
KOMKROWER, G. M. (1951): *Brit. Med. J.*, **2**, 1193.
KRISTENSON, A. (1953): *Acta Med. Scand.*, **145**, 52.
LAVDSBOROUGH, D. (1951): *Brit. Med. J.*, **1**, 884.
LEHMANN, J. (1946): *Lancet*, **1**, 15.
LICHTENSTEIN, M. R., and CANNEMEYER, W. (1953): *J. Amer. Med. Ass.*, **152**, 606.
LIVINGSTONE, R., and STREET, E. W. (1950): *Lancet*, **2**, 308.
LYNCH, M. J. G. (1950): *J. Clin. Path.*, **3**, 114.
MCKECHNIE, J. K. (1953): *Brit. J. Tuberc.*, **47**, 150.
MCKENDRICK, G. D. W. (1951): *Lancet*, **2**, 668.
MCMANIS, A. G., and MIRA, W. J. D. (1951): *Med. J. Aust.*, **2**, 747.
MADIGAN, D. G., GRIFFITHS, L. L., LYNCH, M. J. G., BRUCE, R. A., KAY, S., and BROWNLEE, G. (1950): *Lancet*, **1**, 239.
MANN, B. (1953): *Tubercle*, **34**, 23.
MEDICAL RESEARCH COUNCIL (1950): *Brit. Med. J.*, **2**, 1073; (1952) *ibid.*, **2**, 735; (1953a) *ibid.*, **1**, 521; (1953d) *ibid.*, **2**, 1005.
MURI, A. J. (1952): *Nord. Med.*, **47**, 155.
NAGLEY, M. M. (1949): *Practitioner*, **163**, 459.
NAGLEY, M. M., and LOGG, M. H. (1949): *Lancet*, **1**, 913.
ROWLANDS, S. D. (1953): *Tubercle*, **34**, 143.
RUSSELL, JR., W. F. (1952): *Amer. Rev. Tuberc.*, **66**, 619.
SCOTT, A. B. A., and MCCANN, J. J. (1950): *Lancet*, **2**, 366.
STEEL, S. J. (1952): *Brit. Med. J.*, **1**, 415.
STRONG, J. A. (1951): *Brit. Med. J.*, **2**, 998.
SWANSON, J. N. (1949): *Lancet*, **2**, 175.
THOMAS, J. H. (1952): *Tubercle*, **33**, 329.
WARRING, F. C., and HOWLETT, K. S. (1952): *Amer. Rev. Tuberc.*, **65**, 235.
WHITBY and BRITTON (1950): "Diseases of the Blood," 6th ed., p. 545.
YEH, J. C. (1952): *Canad. Med. Ass. J.*, **67**, 435.

PLEURAL EOSINOPHILIA

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Referring to the cytology of the pleural fluid in serofibrinous pleurisy, Price (1950) states that (*a*) "in rare cases large numbers of eosinophils have been found" and (*b*) "the origin of these cases is at present doubtful." The rarity of the condition is also emphasised by Kirk (1938), who did not find a single instance in 160 cases of pleural effusion examined cytologically, and by Bayne-Jones (1916), who states that from 1 to 5 per cent. of fluids may be eosinophilic, the exact figure depending upon the minuteness of staining and examining the sediment.

There is some uncertainty in the literature regarding the precise definition of eosinophilic pleural fluid. MacMurray, Katz and Zimmerman (1950) consider that a fluid can be termed eosinophilic if 5 per cent. or more of the cells (other than red blood cells) are eosinophils. Most of the reported cases, however, indicate that typical eosinophilic fluid has an eosinophil content of at least 50 per cent. and sometimes as high as 90 per cent. In the present uncertain state of knowledge regarding the significance of eosinophilic fluid, it would seem wise to limit the term to undoubted and striking cases with a high percentage of eosinophils, thus excluding the not uncommon cases in which a few eosinophils, possibly derived from extravasated blood and almost certainly of no special significance, are observed. It is also important, in suspected eosinophilic fluid, to avoid errors in identification of the cells present. This is emphasised, because with Leishman's stain, which is commonly employed for simple cytological investigations, the granules of neutrophil polymorphs may appear unduly pink, thus simulating, on superficial examination, the granules of eosinophils; confusion can be avoided by careful observation for the typical bilobed nuclei of eosinophils. Further, it should be ascertained that the fluid is really pleural fluid; Trail (1943) has pointed out that eosinophilic fluid may be aspirated from a pulmonary hydatid cyst which has been diagnosed in error as a pleural effusion.

This paper is based on a study of 8 cases of pleural eosinophilia encountered during cytological investigation of 253 cases of pleural effusion, an incidence of 3·2 per cent. In all 8 cases the proportion of eosinophils in the pleural fluid was over 50 per cent. It is of interest that no other fluid had an eosinophil content of more than 1 per cent., indicating that when the condition does occur it is likely to be a striking phenomenon. Details of the cases are as follows:

Case 1. E.H., aged 27, gave birth to a child on July 16, 1947. On the fifteenth day of the puerperium she developed acute pleuritic pain in the left chest, followed three days later by hæmoptysis. At this point she was admitted to a medical ward. Clinical and radiological examination of the chest showed

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a small left pleural effusion without evidence of parenchymatous lung disease. Diagnostic aspiration of the pleural fluid gave the following findings: Clear serous fluid with thin clot; cell count 900/cu. mm.; differential count—eosinophils 52 per cent., neutrophils 8 per cent., lymphocytes 18 per cent., endothelials 22 per cent.; ordinary culture—sterile; Lowenstein-Jensen culture—sterile. Aspiration was repeated after three weeks with similar findings, although by now the eosinophils showed marked degenerative changes. Several blood counts showed no blood eosinophilia. X-ray of chest following absorption of the fluid showed no lung pathology. A Mantoux test (1:100) was negative, and has remained so during a five-year follow-up. The final diagnosis was pulmonary embolism with associated pleural effusion following pelvic vein thrombosis.

Case 2. G.S., a male aged 68, was admitted to a medical ward on May 5, 1949. Two days before admission he had developed acute pleuritic pain in the right chest. Clinical and radiological examination of the chest showed a small right pleural effusion without evidence of parenchymatous lung disease. Although the patient had not complained of it, there was also evidence of thrombo-phlebitis of the left leg. Blood count gave W.B.C. 5,000/cu. mm. with normal cell proportions—eosinophils 3 per cent. Diagnostic aspiration of the pleural fluid gave the following findings: Hæmorrhagic fluid with thick clot; protein 5 gm./100 mils.; cell count 1,200/cu. mm.; differential count—eosinophils 56 per cent., neutrophils 20 per cent., lymphocytes 20 per cent., endothelials 4 per cent.; ordinary culture—sterile.

One week after admission he had a further attack of right pleuritic pain followed by hæmoptysis. Further diagnostic aspiration of the pleural fluid again showed a hæmorrhagic exudate; the cell content was now scanty and consisted of a few lymphocytes only. Treatment with anticoagulants was instituted and subsequent progress was uneventful. Follow-up radiology showed no evidence of lung pathology. Although bronchial carcinoma was suspected initially, the final diagnosis was recurrent pulmonary embolism with associated pleural effusion following thrombo-phlebitis of the leg veins.

Case 3. G.M., a male aged 41, was admitted to a medical ward on June 7, 1949. Two weeks previously he had suddenly become ill with shivering, weakness, anorexia and vomiting. One week later, while still confined to bed on sulphonamide therapy, he developed acute pleuritic pain in the right chest with slight cough and mucoid sputum; increasing dyspnœa caused his admission to hospital. Clinical and radiological examination of the chest showed a moderately large right pleural effusion without evidence of parenchymatous lung disease. It was noted that the dyspnœa seemed out of proportion to the amount of fluid present. Blood examination showed W.B.C. 5,400/cu. mm. with normal proportions—eosinophils 4 per cent.; B.S.R. 75 mm. in 1 hour (Westergren). Diagnostic aspiration of the fluid gave the following findings: Clear serous fluid with thick clot; protein 5·78 gm./100 mils.; cell count 1,300/cu. mm.; differential count—eosinophils 70 per cent., neutrophils 5 per cent., lymphocytes 15 per cent., endothelials 10 per cent.; ordinary culture—sterile; Lowenstein-Jensen culture—sterile.

His condition improved with remarkable rapidity; no fluid could be obtained on attempted diagnostic aspiration after one week. At no time in the ward did he have pyrexia or tachycardia. B.S.R. became normal in two weeks. Several specimens of sputum showed no growth of tubercle bacilli on Lowenstein-Jensen culture. Further, a Mantoux test (1:100) was negative and has remained so during follow-up for three years. Follow-up radiology of chest has confirmed the absence of parenchymatous lung disease.

No final diagnosis could be made in this case. Striking features following admission to hospital were the transient nature of the effusion and the absence of toxæmic upset, both of which are unusual in post-primary tuberculous effusion, a diagnosis in any case excluded by the persisting negative Mantoux test. There was no clinical or radiological evidence of hydatid disease. Other serious diseases (*e.g.*, tumour, reticulosis, polyarteritis nodosa) were excluded by follow-up. It might be that he began with a simple inflammatory lung condition which, modified by sulphonamide therapy, resolved during the two weeks prior to his investigation in hospital, but in the meantime produced a sterile inflammatory effusion.

Case 4. N.B., female, aged 17, developed a left pleural effusion following thoracotomy for closure of a patent ductus arteriosus on December 9, 1949. Diagnostic aspiration showed a heavily blood-stained fluid with thick clot; it contained 60 per cent. eosinophils and 40 per cent. endothelials and was sterile on culture. Examination of the peripheral blood was not done. No doubt the origin of the effusion was partly traumatic and partly irritative from the presence of blood in the pleural cavity.

Case 5. A.M., male, aged 40, was admitted to a medical ward on November 29, 1949. Six weeks before he had developed mild left renal colic associated with bladder pain on micturition. He was off work during the six weeks without special treatment from his family doctor. Three days before admission he developed another pain, this time typically pleuritic in type and situated over the left lower ribs posteriorly; there was also some cough with mucoid sputum, but no shivering or fever. Clinical and radiological examination of the chest revealed a small left pleural effusion without evidence of parenchymatous lung disease. Clinical examination of the genito-urinary tract was negative; urine contained no albumin, crystals or pus cells and was sterile on culture. Blood examination showed W.B.C. 6,200/cu. mm. with normal proportions —eosinophils 2 per cent.; B.S.R. 82 mm. in 1 hour (Westergren). Diagnostic aspiration of the pleural fluid gave the following findings: Clear serous fluid with thin clot; cell count 1,100/cu. mm.; differential count—eosinophils 58 per cent., neutrophils 8 per cent., basophils 2 per cent., lymphocytes 10 per cent., endothelials 22 per cent.; the endothelial cells were notably large with prominent nuclei and showed a tendency to aggregate into clumps; ordinary culture—sterile; Lowenstein-Jensen culture—sterile.

During a stay of seven weeks in the ward he remained apyrexial with slight tachycardia (80-90/min.). B.S.R. remained elevated at 70 mm. in 1 hour. The pleural fluid absorbed very slowly; repeat diagnostic aspiration after one month showed no appreciable change in cytology from the original findings. There was no recurrence of urinary symptoms and complete urological investigation showed no abnormality of the urinary tract. Numerous specimens of sputum and a 24-hour specimen of urine were negative on culture for tubercle bacilli. Mantoux (1:100) was positive.

He was discharged from hospital on January 16, 1950. After a short spell of convalescence, the pleural fluid absorbed completely and B.S.R. fell rapidly to normal. During follow-up for two and a half years he has remained extremely well and serial X-rays of chest have revealed nothing apart from residual pleural thickening at the site of the effusion.

As in case 3, a final diagnosis could not be made. Tuberculosis could not be excluded as a cause of the pleurisy with effusion, but the history of onset was not typical of tuberculosis. The unusual endothelial cells in the fluid raised a suspicion of neoplasm, but follow-up has excluded this possibility. It is possible that he had a urinary infection prior to admission with spread of

infection from the left kidney, where the original pain was maximal, through the perinephric tissues and diaphragm to the left pleural cavity; the indolent nature of the effusion with long-continued elevation of B.S.R. is, however, somewhat against such a simple sterile inflammatory effusion.

CASE 6. W.P., male, aged 27, was admitted to a medical ward on December 13, 1949. Four weeks before admission, while sitting in a cinema, he developed sudden left pleuritic pain. On going home to bed he felt shivery and fevered. Some cough and mucoid sputum appeared the next day. His doctor kept him at rest in bed. For some months prior to his illness he had felt easily tired and had become thinner. Clinical and radiological examination of the chest showed a small left pleural effusion without evidence of parenchymatous lung disease, although on the X-ray both hilar shadows were abnormally prominent. Blood examination showed W.B.C. 7,400/cu. mm. with normal proportions—eosinophils 5 per cent.; B.S.R. 12 mm. in 1 hour (Westergren). Diagnostic aspiration of the fluid gave the following findings: Clear serous fluid with thin clot; cell count 800/cu. mm.; differential count—eosinophils 76 per cent., neutrophils 0 per cent., basophils 1 per cent., lymphocytes 20 per cent., endothelials 3 per cent.; ordinary culture—sterile; Lowenstein-Jensen culture—sterile. Numerous specimens of sputum were negative on culture for tubercle bacilli. Mantoux (1: 1,000) was positive.

He was in the ward for one week, during which temperature and pulse remained normal. He was then transferred to a convalescent hospital where further progress was satisfactory and he was discharged home on April 11, 1950.

Unfortunately, on May 6, 1950, left pleuritic pain recurred with formation of a further pleural effusion. B.S.R. was 12 mm. in 1 hour. Diagnostic aspiration as an out-patient gave the following findings: Heavily blood-stained fluid with thick clot; cell count—not done; differential count—lymphocytes 75 per cent., neutrophils 10 per cent., eosinophils (disintegrating) 10 per cent., endothelials 5 per cent.; ordinary culture—sterile; Lowenstein-Jensen culture—sterile. The second pleurisy subsided rapidly with rest in bed at home. He has remained well for two years and serial chest X-rays show slight residual pleural thickening.

Although no positive proof was forthcoming, the whole course of the illness in this case was highly suggestive of a tuberculous etiology. It should be noted that the first diagnostic aspiration was performed four weeks after the initial pleurisy. It is of interest that the second pleurisy six months after the first gave a blood-stained effusion with reduction in eosinophil content from 76 per cent. to 10 per cent.

CASE 7. T.M., male, aged 32, was admitted to a medical ward on July 4, 1950. His history was typical of lobar pneumonia. Clinical and radiological examination of the chest showed a right lower lobe consolidation with a small overlying right pleural effusion. His own doctor had already treated him with penicillin and sulphonamide. Blood examination showed W.B.C. 7,400/cu. mm. with normal proportions—eosinophils 2 per cent.; B.S.R. 58 mm. in 1 hour (Westergren). Diagnostic aspiration of the pleural fluid gave the following findings: Clear serous effusion with thick clot; cell count 1,700/cu. mm.; differential count—eosinophils 82 per cent., basophils 1 per cent., neutrophils 0 per cent., lymphocytes 13 per cent., endothelials 4 per cent.; ordinary culture—sterile; Lowenstein-Jensen culture—sterile. Bacteriological examination of sputum showed a mixture of organisms but no tubercle bacilli. Progress in the ward was entirely satisfactory and X-ray of chest prior to discharge showed almost complete disappearance of the consolidation and fluid. He has remained well over a two-year follow-up.

The final diagnosis was right lower lobe pneumonia with a sterile syn-pneumonic pleural effusion.

Case 8. A.G., female, aged 51, was admitted to a medical ward on July 27, 1950. Four weeks before admission she had developed acute pleuritic pain in the right chest followed by pain and swelling in the left leg. Clinical examination revealed an extensive thrombo-phlebitis of the left leg and a small right pleural effusion. Radiological examination of the chest confirmed the presence of a right pleural effusion with some underlying opacity in the right lower lobe. Blood examination showed W.B.C. 9,200/cu. mm. with normal proportions—eosinophils 4 per cent. Diagnostic aspiration of the pleural fluid gave the following findings: Slightly cloudy fluid (not blood-stained); protein 8 gm./100 mil.; cell count—not done; differential count—eosinophils 55 per cent., neutrophils 10 per cent., lymphocytes 35 per cent.; ordinary culture—sterile; Lowenstein-Jensen culture—sterile. The sputum was also negative on culture for tubercle bacilli. While in the ward she was apyrexial with a normal pulse rate. The thrombo-phlebitis subsided with anti-coagulant therapy and the pleural effusion absorbed. She was was discharged after one month. Six months later she had no abnormal symptoms or signs and chest X-ray showed only residual pleural thickening in the right costo-phrenic angle. The final diagnosis was pulmonary embolism with associated pleural effusion following thrombo-phlebitis of the leg veins.

Comments on the Eight Cases

In 5 (Nos. 1, 2, 4, 7 and 8) of the 8 cases, the etiology of the pleural effusion was definitely established—viz., pulmonary infarction (3 cases), lobar pneumonia (1 case) and post-thoracotomy (1 case). In the remaining 3 cases the etiology could not be established; in 1 case (case 3), tuberculosis could be excluded on the basis of a persistently negative Mantoux test, and the course of the illness suggested a simple inflammatory condition; in another (case 6) tuberculosis, although not proved, seemed the most probable etiological factor; in the third (case 5) the evidence was equally balanced between a simple inflammatory and tuberculous etiology. In no case was there evidence either at the time or on subsequent follow-up of "eosinophilic lung," polyarteritis nodosa, blood dyscrasia, reticulosis, neoplasm, parasitic infection or "allergic diathesis."

All the fluids were sterile on ordinary culture. Two (case 2, pulmonary infarction, and case 4, post-thoracotomy) were heavily blood-stained on initial aspiration. The remaining 6 (Nos. 1, 3, 5, 6, 7 and 8) were clear and serous or only slightly cloudy. The clot formation and/or protein estimation indicated that in each case the fluid was an exudate rather than a transudate, while the differential cell count revealed the striking preponderance of eosinophils; in three cases (Nos. 5, 6 and 7) there was also an appreciable number of basophils. Repeat diagnostic aspiration was performed after an interval of from one to four weeks in three cases: in case 1 (pulmonary infarction) and case 5 (diagnosis uncertain), the fluid was macroscopically and cytologically unchanged; in case 2 (pulmonary infarction) the eosinophilic exudate had changed to a lymphocytic exudate. In another case (case 6—probably tuberculous), pleurisy with effusion recurred after an interval of six months; the fluid, initially clear and serous, was now found to be blood-stained, and the content of eosinophils had fallen from 76 per cent. to 10 per cent.

It must be emphasised that in 7 of the 8 cases so investigated there was no eosinophilia or even leucocytosis in the peripheral blood either during the formation or absorption of the eosinophilic pleural fluid.

Discussion

A. From the practical point of view the main interest of eosinophilic pleural effusion lies in the question of whether or not it has any diagnostic or prognostic significance in the individual case. It is proposed to discuss this in relation to various possible etiological factors:

(*a*) *Pneumonia.* One case of the present series developed a sterile eosinophilic pleural effusion during the course of a lower lobe pneumonia. Bayne-Jones (1916) describes a similar case in detail and refers to 8 others within his experience. Close (1946) refers to 2 cases who gave histories of " recurrent pneumonia " over a period of five years. " Pulmonary congestion "—probably pneumonia—is given as a cause by Faure-Beaulieu (1938), 1 case, and Mosny and Portocalis (1913), 2 cases. Ellis (1945) states that " the presence of eosinophils in the uncommon clear effusion following pneumonia indicates the probability that the fluid will not become purulent," a point previously noted by Trail (1943).

(*b*) *Pulmonary Infarction.* Three cases of the present series developed eosinophilic pleural effusion following pulmonary infarction. There is no previous reference to this occurrence in the literature.

(*c*) *Trauma.* One case of the present series developed a sterile blood-stained eosinophilic pleural effusion following thoractomy for the closure of a patent ductus arteriosus. Possibly this is an example of operative trauma and is analogous to the pleural eosinophilia described by Gregoire and Courcoux (1919) in relation to traumatic hæmothorax.

(*d*) *Tuberculosis.* Ellis (1945) states that " the presence of eosinophils in any number is usually evidence against the infection being tuberculous." On the other hand, Gill (1940) describes a case of abdominal and pleural tuberculosis proved by necropsy in which the pleural fluid contained 80 per cent. eosinophils; he also refers to three other tuberculous cases described in the literature and draws attention to the fact that eosinophils may be found in effusions complicating artificial pneumothorax therapy for pulmonary tuberculosis; in the latter, according to Pavie, Lefèvre and Rossignol (1937), who produced pleural eosinophilia in a healthy rabbit by inducing a pneumothorax, trauma to the pleura may be a factor. MacMurray, Katz and Zimmerman (1950) state that pleural eosinophilia may occur in tuberculous effusion, but that it never occurs early in the course of the disease; by this statement they presumably mean that it does not occur in the common type of post-primary tuberculous effusion.

During the collection of the present series of cases, pleural fluid from 253 cases was examined cytologically. Of the 253 cases, 102 were finally regarded as tuberculous or probably tuberculous in origin; of those 102 cases, only one —an unproved case—showed pleural eosinophilia. In one further case showing pleural eosinophilia, tuberculosis was a possible but not a probable diagnosis. It is therefore concluded, both from this study and from the review of the

literature, that pleural eosinophilia is a most uncommon finding in tuberculous pleural effusion.

(*e*) "*Eosinophilic Lung.*" Nagel (1941) describes a case of Loeffler's syndrome complicated by a massive pleural effusion in which blood eosinophilia reached 9 per cent. and fluid eosinophilia 83 per cent. Baumann (1944) describes a similar case presenting with chest symptoms in which both sputum and pleural fluid contained a high proportion of eosinophils; the W.B.C. count in the peripheral blood was 14,500/cu. mm. with 25 per cent. eosinophils; later the patient passed ova of *Ascaris lumbricoides* in the stool. Harkavy (1941), writing on vascular allergy, refers to 8 cases of asthma associated with pulmonary infiltrations and blood eosinophilia; of the 8 cases, 6 had effusion into one or both pleural cavities, the eosinophil content varying from 85 per cent. to 100 per cent. Crofton, Livingstone, Oswald and Roberts (1952) believe that pleural effusion containing a high proportion of eosinophils may occur in any of the subgroups of "pulmonary eosinophilia"—*e.g.*, Loeffler's syndrome, Weingarten's syndrome, polyarteritis nodosa; they further point out that on occasion the effusion may obscure an underlying pulmonary lesion in the chest X-ray, thus causing the case to present as one of primary eosinophilic pleural effusion.

Only if eosinophilia is detected in the peripheral blood can a diagnosis of "pulmonary eosinophilia" be entertained. In the present series of cases there was none with blood eosinophilia and none with suggestive radiological changes in the lungs. From the practical point of view it should be kept in mind that "pulmonary eosinophilia" is not only uncommon in Great Britain, but it is also uncommon for it to cause a pleural effusion.

(*f*) *Hydatid Disease.* Ellis (1945) states that "a combination of true eosinophilia in pleural fluid and peripheral blood is usually presumptive evidence of hydatid disease."

(*g*) *Miscellaneous Conditions.* Isolated cases of pleural eosinophilia have been described in association with Hodgkin's disease (MacMurray, Katz and Zimmerman, 1950), generalised dermatitis (Close, 1946), bronchial carcinoma (Bernard, Marie and Anchel, 1931), "hay fever diathesis" (MacMurray, Katz and Zimmerman, 1950), and amœbic abscess of the lung (de Lavergne, Abel and Debenetti, 1930). References to Hodgkin's disease, generalised dermatitis and "hay fever diathesis" are not surprising in view of the known association of eosinophilia with those conditions. It is of interest that the reference to bronchial carcinoma is the only one in the literature associating pleural eosinophilia with tumour. Cases in which a final diagnosis could not be made are also mentioned by Crofton, Livingstone, Oswald and Roberts (1952), Reinikainen (1947) and Punch and Close (1938).

This review of possible etiological factors in eosinophilic pleural effusion indicates that from the diagnostic point of view in the individual case certain tentative suggestions can be made. If blood eosinophilia coexists with the pleural eosinophilia, the patient should be investigated for the presence of hydatid disease, "pulmonary eosinophilia" (Loeffler's syndrome, Weingarten's syndrome, polyarteritis nodosa) and possibly Hodgkin's disease. If there is no blood eosinophilia, pulmonary infarction, trauma to the pleura

and pneumonia should be considered in diagnosis. (Although, for convenience, two groups of conditions depending on the presence or absence of blood eosinophilia have been given, it is not suggested that the distinction is absolute.) Malignant disease is an improbable diagnosis in the presence of pleural eosinophilia. Tuberculosis cannot be excluded as a cause, but the available evidence suggests that it should not be readily diagnosed unless other strong evidence is forthcoming. Finally, too much significance should not be attached to the presence of blood in the fluid (*vide infra*).

From the prognostic point of view little can be said, since so much depends on the ultimate diagnosis. Ellis (1945) and Trail (1943) state that in eosinophilic effusion due to lobar pneumonia empyema is most unlikely to develop. MacMurray, Katz and Zimmerman (1950) state that most eosinophilic effusions are transient in nature and pursue a benign course. In the present series of cases, all certainly pursued a relatively benign course, but only two could be called transient.

B. *The Mechanism of Production of Pleural Eosinophilia.* Although in some cases—*e.g.*, " pulmonary eosinophilia," hydatid disease—pleural eosinophilia may be part of a generalised disturbance, the absence, in the present series of cases, of blood eosinophilia, suggests that the cause is often localised to the pleural cavity. It is tempting to assume with Bayne-Jones (1916) the presence of an eosinotactic substance in the pleural exudate. If such a substance exists, it must do so as a largely non-specific phenomenon common to a variety of pathological processes in the pleural cavity. It has been pointed out by Crofton, Livingstone, Oswald and Roberts (1952) and MacMurray, Katz and Zimmerman (1950) that approximately two-thirds of the cases described in the literature have been associated with hæmorrhagic pleural fluid. Hæmorrhage, however, cannot be the only factor, since only 2 of the 8 cases in the present series had blood-stained fluid initially. Furthermore, numerous cases of hæmorrhagic fluid without associated pleural eosinophilia have been observed in malignant disease. In case 6 with an initially clear fluid, the development of hæmorrhagic fluid was associated with a striking fall in the eosinophil content. The association with traumatic hæmothorax (Gregoire and Courcoux, 1919), pleural fluid complicating artificial pneumothorax (Pavie, Lefèvre and Rossignol, 1937), thoracotomy and pulmonary infarction, suggests that trauma to the pleura, possibly associated with hæmorrhage, may be a factor in some cases. Occasionally the eosinophilic exudate has in the course of time given way to a lymphocytic exudate (Harvier and Mallarmé, 1937); case 2 of the present series. This may have no significance, but it may suggest that lymphocytes and eosinophils have an obscure interrelationship; in this connection Blalock, Robinson, Cunningham and Gray (1937) have observed that complete lymphatic blockage in the dog leads to disappearance in the blood not only of lymphocytes but also of eosinophils. It is clear that the immediate causation of pleural eosinophilia, although a fruitful subject for speculation, is ill-understood and requires further investigation. Another obscure problem is the occasional presence of a small number of basophils along with the eosinophils. This was observed in 3 cases of the present series and has previously been reported by Mosny and Portocalis (1913) and Bayne-Jones (1916).

Summary

1. Eight cases of pleural eosinophilia are described.
2. The diagnostic significance of pleural eosinophilia is discussed.
3. Attention is drawn to pulmonary infarction as a cause of pleural eosinophilia.

REFERENCES

BAUMANN, H. (1944): *Schweiz. med. Wschr.*, **74,** 326.
BAYNE-JONES, S. (1916): *Johns Hopk. Hosp. Bull.*, **27,** 12.
BERNARD, L., MARIE, J., and ANCHEL, J. (1931). *Bull. Soc. méd. Hôp. Paris*, **47,** 1610.
BLALOCK, A., ROBINSON, C. S., CUNNINGHAM, R. S., and GRAY, M. E. (1937): *Arch. Surg., Chicago*, **34,** 1049.
CLOSE, H. G. (1946): *Lancet*, **1,** 193.
CROFTON, J. W., LIVINGSTONE, J. L., OSWALD, N. C., and ROBERTS, A. T. M. (1952): *Thorax*, **7,** 1.
ELLIS, R. (1945): *Med. Pr.*, **213,** 122.
FAURE-BEAULIEU (1938): *Progr. méd., Paris*, **48,** 1599.
GILL, A. M. (1940): *Brit. med. J.*, **2,** 220.
GREGOIRE, N., and COURCOUX, A. (1919): "Wounds of the Pleura and Lung." London.
HARKAVY, J. (1941): *Arch. intern. Med.*, **67,** 709.
HARVIER, P., and MALLARMÉ, J. (1937): *Paris méd.*, **2,** 67.
KIRF, R. C. (1938): *J. Lab. clin. Med.*, **23,** 1137.
DE LAVERGNE, V., ABEL, E., and DEBENETTI, R. (1930): *Paris méd.*, **2,** 67.
MACMURRAY, F. G. KATZ, S., and ZIMMERMAN, H. J. (1950): *New Engl. J. Med.*, **243,** 330.
MOSNY, E., and PORTOCALIS, A. (1913): *J. Physiol. Path. gén.*, **15,** 120.
NAGEL, O. (1941): *Beitr. Klin. Tuberk.*, **96,** 185.
PAVIE, P., LEFEVRE, P., and ROSSIGNOL, G. (1937): *Presse méd.*, **45,** 494.
PRICE, F. W. (1950): "A Textbook of the Practice of Medicine," 8th ed. p. 1314.
PUNCH, A. L., and CLOSE, H. G. (1938): *Guy's Hosp. Rep.*, **88,** 143.
REINIKAINEN, M. (1947): *Ann. Med. intern. fenn.*, **36,** 145.
TRAIL, R. R. (1943): *Brit. med. J.*, **1,** 98.

COSTO-CLAVICULAR SYNDROME AS A SEQUEL TO ARTIFICIAL PNEUMOTHORAX

By James Maxwell

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The complications of artificial pneumothorax treatment have been described in numerous papers but little has been written upon the subject of sequelæ. In most cases the patient is symptom-free after the cessation of refills in a successful case but occasionally there may be a slight contraction of the chest on the treated side and symptoms may result from this. It is the purpose of this paper to draw attention to the fact that a comparatively slight alteration in the shape of the upper part of the thorax may occasionally lead to the development of extra-thoracic symptoms. Two cases are described here in which the termination of an artificial pneumothorax was quickly followed by the development of a typical ulnar nerve syndrome.

Case 1, female, æt. 27 years, was seen at the Royal Chest Hospital in February 1929, when she was found to have bilateral pulmonary tuberculosis. She was admitted to a sanatorium and the disease rapidly became quiescent. The lesions in the left lung healed without difficulty, but there was a small persistent cavity in the right upper lobe. An artificial pneumothorax was induced in December 1930 and refills were carried out until March 1934. Towards the end of treatment she developed a little fluid in the pleura, although this was never sufficient to interfere with the function of the pneumothorax. In June 1934 the patient began to complain of pain in the right arm and this rapidly increased in severity. Within a month of the onset of the pain there was obvious weakness of the muscles supplied by the ulnar nerve. There were also anæsthesia and analgesia, particularly in the distribution of the first dorsal segment. Marked wasting of the small muscles of the right hand, especially the first dorsal interosseus and the abductor pollicis, appeared within a few weeks. The X-ray film showed a pair of quite short cervical ribs. There were no symptoms on the left side.

It was considered that this was a typical ulnar nerve syndrome, due to the presence of the cervical rib, and an exploratory operation was performed in November 1934.

The usual incision was made at the outer border of the anterior scalene muscle and the cords of the brachial plexus were isolated. The small cervical rib was not very apparent, and the scalenus anticus did not appear to be causing any interference with the plexus. A very firm fibrous band was, however, found to be causing pressure on the outer part of the lower cord in the scalenus medius. This band and a portion of the muscle were divided. It was noted during the operation that the subclavian artery appeared to be higher than normal and this was thought to be due to dropping of the right shoulder.

The result of the operation was immediate relief of the symptoms. The sensory disturbance disappeared at once and the muscle power was completely

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regained within a few months. The patient has been under observation since the time of the operation and there has been no recurrence of symptoms.

Case 2, female, æt. 32, was seen in May 1942, when a diagnosis of active tuberculosis in the left upper lobe was made. An artificial pneumothorax was induced and the patient was transferred to a sanatorium, where a phrenic avulsion was performed in October 1942; the reason for this procedure is not clear. Refills were continued without incident until the onset of an obliterative pleurisy caused the pneumothorax to be abandoned in June 1945. At this stage it appeared that the disease in the lung was soundly healed and, in fact, the patient has not subsequently suffered any ill-health. Nevertheless, the obliterative pleurisy resulted in a considerable fibrosis and contraction of the whole of the left lung. In March 1946 the patient began to experience pain along the inner border of the left arm, and an X-ray at the local hospital disclosed a short cervical rib on the left side. Neurological examination revealed slight loss of sensation in the distribution of the ulnar nerve, and there was a little motor weakness but no muscle wasting. It was noted in this case that abduction of the left arm caused marked diminution in the volume of the pulse.

An exploratory operation was carried out in April 1946. An incision was made one inch above and parallel with the clavicle. The scar of the phrenic operation was excised. The scalenus anterior muscle was seen to be compressing the subclavian artery and, on division of this muscle, a fibrous band was felt in the scalenus medius, running downwards and outwards in line with the lateral border of the scalenus anticus. This fascial band was lifting the lower trunk of the brachial plexus, compressing both the artery and the nerve against the posterior surface of the scalenus anticus. On division of the band the nerve and artery fell back into their normal place. There was no apparent cervical rib, nor was there any thickened band representing the scalenus pleuralis.

In this case also there was immediate relief of symptoms. The patient has been kept under observation since the time of operation and she has remained well.

Discussion

A number of papers have been published in the last fifteen years on the subject of pain in the arm resulting from abnormalities in the costo-clavicular space. It is many years since Todd (1912) pointed out that dropping of the shoulder determines the onset of symptoms of nerve pressure by causing the nerves in the plexus to be stretched over the abnormal bony process. Wright (1945) described a neurovascular syndrome which is produced by hyperabduction of the arm. He drew special attention to the changes which might follow obstruction of the subclavian artery, and he attributed the sensory changes to stretching and ischæmia of the brachial plexus trunks. According to Wright there are two zones in which stretching and torsion may take place: (*a*) the point at which the axillary-subclavian vessels and the trunks of the brachial plexus pass beneath the coracoid process and behind the pectoralis minor muscle, and (*b*) the point at which the subclavian vessels and the trunks of the plexus pass behind the clavicle and the first rib. Wright was of the opinion that symptoms were likely to result from the adoption of a bad sleep posture, the patient sleeping in the supine position with the arms hyperabducted. A detailed consideration of the mechanism of pain in the upper limb resulting from abnormalities in the costo-clavicular space was presented

by Stammers (1950), who based his observations on a series of forty cases. He also considered the factors which are mainly concerned in producing symptoms. Anatomical variations in the composition of the brachial plexus, and in the distribution of the sympathetic nerve fibres in particular, may play some part. It appears to be a fairly common experience at operation to discover the existence of a fibrous band in the inner border of the scalenus medius muscle, with the inner cord of the plexus or the highly arched subclavian artery kinked against it.

An abnormal first thoracic rib may be present, but it may be very difficult to distinguish this from a cervical rib, according to White (1945), unless a special radiographic technique is employed. Annersten (1947) considers that compression of the artery or cord between the scalenus anticus and an enlarged seventh cervical transverse process is the important feature in the production of symptoms.

Rogers (1949) discussed the cause of upper limb pain due to lesions of the thoracic outlet. He concluded that the scalenus syndrome is of commoner occurrence than cervical rib in producing pain in the arm, and that it is not enough merely to divide the scalenus anticus, because the lowest trunk of the brachial plexus may still suffer stretching or compression.

It would certainly appear, from consideration of the two cases described here, that contraction of the upper part of the thoracic cage may occasionally cause a drop in the mobile structures which occupy the costo-clavicular space and that this alteration in anatomical relationship may be sufficient to determine the onset of symptoms. It is probably more than a coincidence that an anatomical bony abnormality was demonstrable in this region in both cases, and it would appear reasonable to deduce that a moderate amount of contraction will not produce this syndrome unless such an abnormality is present. The development of the syndrome is therefore unlikely to occur very often as a sequel of pneumothorax treatment, because there must be a combination of factors present before compression can take place. The development of pain in the arm on the side which has been treated by artificial pneumothorax is an indication that this syndrome is occurring. Early operation for the relief of pressure is likely to be followed by a speedy cure of the condition.

Summary

Very occasionally a " costo-clavicular syndrome " may occur soon after an artificial pneumothorax is abandoned. It is more likely to occur when there is an anatomical abnormality in the bones of the neck, and when there is a more than average degree of contraction of the upper part of the chest. It can be completely relieved by early operation.

REFERENCES

ANNERSTEN, S. (1947): *Acta Chir. Scand.*, **95**, 419.
ROGERS, L. (1949): *Brit. Med. J.*, **2**, 956.
STAMMERS, F. A. R. (1950): *Lancet*, **1**, 603.
TODD, R. (1912): *Anat. Anzeiger*, **14**, 385.
WRIGHT, I. S. (1945): *Amer. Heart J.*, **29**, I.

CHEST SEQUELÆ OF INFECTIOUS DISEASES

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Of all the common infectious diseases which may initiate chronic chest disease perhaps the two worst offenders are measles and whooping cough, and especially the two in combination when they appear concurrently in a young child. Pneumococcal and other acute bacterial pneumonia and recurrent acute bronchitis are also potent contributors to pulmonary sequelæ but, owing to the difficulty of obtaining accurate histories, the extent of the damage they do is less certain. Epidemic influenza with its specific tracheo-bronchitis, its necrosis of ciliated epithelium, and its increased mucus secretion and retention, lays the foundation for bacterial invasion of the lung, especially in the grave form of influenza virus-staphylococcal pneumonia. This condition, if not rapidly fatal, may set up an undetermined amount of pulmonary fibrosis. But the chief rôle of influenza in the establishment of chest sequelæ probably lies in the aggravation of already impaired cardio-respiratory function in older people with production of chronic respiratory catarrh and slow congestive or peripheral heart failure.

Sulphonamides and antibiotics have been singularly successful in the prevention and treatment of measles pneumonia and in the treatment of all forms of bacterial pneumonia, thus materially reducing pulmonary sequelæ from these sources. Their success, however, has been strictly limited in whooping cough, which still remains a formidable menace.

Whooping Cough

Atelectasis and Pneumonia.—There are two types of bronchopneumonia in whooping cough. The first is the early capillary bronchitis and bronchopneumonia which may appear in the second or third week in infants and young children. It is often severe, with respiration rates up to 80 or 90 per minute. There are fine râles and rhonchi scattered diffusely over the middle and lower zones, but there is little or no abnormal shadowing in the lung fields in radiographs. This early bronchopneumonia may be amenable to large doses of penicillin, but more frequently one of the oral antibiotics is required, especially when *H. influenzæ* is a dominant organism in the sputum or laryngeal swab. This form does not appear to be a serious contributor to pulmonary sequelæ. The second form occurs later and is associated with lobular, segmental or lobar pulmonary collapse due to bronchial occlusion with the tough, viscid mucus so characteristic of whooping cough from the third week onwards. The collapsed areas are well seen in postero-anterior and lateral radiographs (Fig. 7) as triangular or irregular patchy shadows filling the cardiophrenic angles, or corresponding to anatomical segments or lobes. Radiographically a distinction between patches of pneumonia and of

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collapsed lung is not always possible, and, in fact, bronchopneumonia and collapse are often present together at this stage of whooping cough. The sites of collapse are nearly always in the left or right lower lobes or both, but the middle lobe is also frequently affected, and the lingula process and upper lobes rarely. Treatment of combined bronchopneumonia and extensive atelectasis is difficult. Antibiotics and the oxygen tent are required for the former, and postural drainage as soon as it can be applied, for the latter. Effective postural drainage must often be withheld in the acute stage until temperature and respiration rates are near normal, and this period of waiting may be inimical to the ultimate clearing of the collapse. The main problem is drainage of the lower lobes, since middle, lingula and upper lobe collapse in whooping cough nearly always clears up spontaneously with little likelihood of bronchiectasis supervening. The child should be laid over a steep double-inclined plane, like the Brompton frame, frequently for periods of 20 minutes, and the foot of the bed should be raised at least 20 inches during the night and, if possible, during the day as well. If this treatment does not show signs of succeeding after four to eight weeks, repeated bronchoscopy and suction are indicated. My experience of bronchoscopy and suction at an earlier stage than this is not encouraging. It is only the exceptional case in which vigorous measures of postural drainage fail to clear the collapse within a few weeks or months. When re-expansion is delayed for two months or more, a bronchogram is advisable, although again it is only in a small minority that bronchiectasis becomes permanent.

Atelectasis without Pneumonia.—This is a relatively common condition which, in the absence of urgent acute symptoms, may remain undiagnosed until permanent bronchiectatic changes have set in. These insidious cases must be looked for carefully from about the fourth week of whooping cough onwards. The child is usually ambulant but fretful; he has lost some of his liveliness and energy and he tends to " lie about "; coughing and vomiting persist, usually with considerable quantities of mucus expelled or swallowed; the respiration rate is raised and slight cyanosis may be detected apart from the paroxysms; an occasional spike of pyrexia may be found. Chest radiographs in such cases may reveal small irregular shadows filling the cardiophrenic angles and sometimes larger shadows of segmental collapse. Postural drainage should at once be instituted and continuous supervision maintained until radiographs are clear. This is an important matter of public health, for a relatively large section of the child population is involved, and it may be largely from this neglected mass that bronchiectasis following whooping cough arises.

Whooping Cough and Tuberculosis.—Unhealed primary tuberculosis is usually aggravated by an attack of whooping cough. The most common clinical manifestation is a flaring up of an unsuspected and unhealed primary complex in a child. The temperature rises unexpectedly without significant chest signs; it is not controlled by antibiotics, and the child remains fretful and ill; a Mantoux test is strongly positive; an older child may show a preliminary erythema nodosum; repeated gastric washings may reveal tubercle bacilli, or they may all be negative; serial radiographs of the chest generally show an enlarging hilar gland shadow, occasionally a few miliary foci, or a hilar " flare " with some upper, middle, or lingula lobe collapse; tuberculous menin-

gitis is a further possible development. A careful history and radiological investigation of contacts usually reveal an open source of infection. Lastly, there is the therapeutic test. Such a case responds within a few days to streptomycin and isonicotinic hydrazide, and a full course of four to six months of these drugs is indicated. Rarely a spasmodic cough resembling that of whooping cough can be simulated by pressure of an enlarging tuberculous hilar gland on the main bronchus. Differential diagnosis in such cases depends on careful assessment of the cough and its course, a white blood count for the relative and absolute lymphocytosis of whooping cough and a cough-plate or pernasal swab for *H. pertussis* within the first four weeks from onset of the cough (Fig. 8).

Empyema is a very uncommon sequela of the bronchopneumonia of whooping cough. *Pneumothorax* and *mediastinal and subcutaneous emphysema* are rare sequelæ, associated with the mechanical strain of the cough.

Measles

Atelectasis and Bronchiectasis.—Epidemics of measles in Great Britain are much milder than they were in the first thirty-five years of the century. Prior to the year 1935, an acute interstitial form of pneumonia following measles could be seen in London hospitals, sometimes accompanied by intense toxæmia and heliotrope cyanosis as in the influenza pandemic of 1918. This had all the characteristics of a severe pneumonitis with intense lymphocytic infiltration of the walls of the bronchioles and alveoli, accompanied by endothelial and fibroblastic proliferation to such an extent as to render many alveoli airless. Mortality was high. Ellison (1931) recorded 47 deaths among 100 cases of measles pneumonia occurring at the Grove Hospital, London, during the 1927-28 epidemic. He also described this acute interstitial type of pneumonia complicating measles at that time and its apparent association with *H. influenzæ* which he recovered from 23 cases by lung puncture. In recovered cases acute bronchiectasis developing in a few weeks was sometimes seen, especially in those with combined measles and whooping cough. Doubtless also, chronic pulmonary sequelæ developed in later life. Kitcat and Sellors (1928), in a series of 53 cases of non-tuberculous pulmonary fibrosis in children under 15 years seen at the Brompton Hospital, attributed the condition to measles in 14 cases (26 per cent.), to whooping cough in 8 cases (15 per cent.) and to a combination of both in 16 cases (30 per cent.). Twenty years later at the same hospital, Oswald (1947) found a marked change as far as measles was concerned. In a series of 50 cases of collapse of the lower lobes in children he found only 4 cases (8 per cent.) due to measles, 7 cases (14 per cent.) due to whooping cough and as many as 17 cases (34 per cent.) due to pneumonia and 13 cases (26 per cent.) due to bronchitis. Thus, while whooping cough remains a major factor in the production of pulmonary sequelæ, measles, as a precursor of collapse at least, has markedly declined and pneumonia and bronchitis have stepped into a premier place.

Important factors influencing the incidence of chronic pulmonary sequelæ after measles include: (1) the severity of recent measles epidemics, especially with reference to the occurrence of interstitial pneumonia, (2) age at the time

of the attack, especially if under 2 years, and (3) history of respiratory disease, especially pneumonia, prior to the attack of measles. Westwater (1933) in a follow-up study of 193 cases of measles treated at the Park Hospital emphasised the last as well as the age factor. In nearly half the cases the susceptibility to recurrent pulmonary trouble had already been acquired prior to the attack of measles. The age factor was specially emphasised in Oswald's series, in which more than half of the children had a history of recurrent pneumonia and bronchitis dating from an acute pulmonary infection during the first 2 years of life. The small calibre of the bronchi at this age must facilitate bronchial occlusion with absorption-collapse, whether produced by measles, whooping cough, pneumonia or bronchitis.

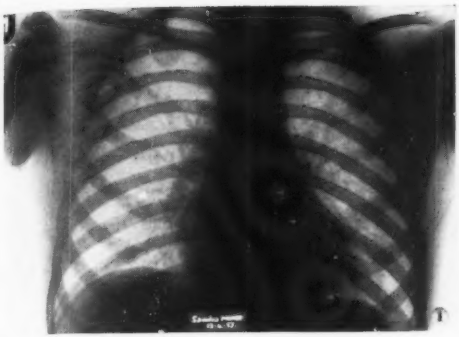
Measles and Tuberculosis.—Unhealed pulmonary tuberculosis, whether primary complex or fibrocaseous phthisis, is very definitely aggravated by measles. Examples of the sequence of events when primary complex and measles are concurrent are shown in Figs. 1-6. It is important to remember that a negative Mantoux test may be unreliable for some three weeks or more after measles. Bentzon (1953) studied tuberculin allergy in certain infectious diseases, and confirmed that the depression of allergy after measles was marked up to nine days after the appearance of the rash, and might be recognisable for three to ten weeks; in scarlet fever it was definite but not so marked as in measles, and in infectious mononucleosis it was evident only in a small proportion of cases, and not necessarily in those exhibiting a rash. On the other hand, no depression of allergy was found after upper respiratory tract infections, acute tonsillitis, pneumonia and dysentery. Failure to allow for this factor may delay the recognition of reactivated primary complex during measles and scarlet fever.

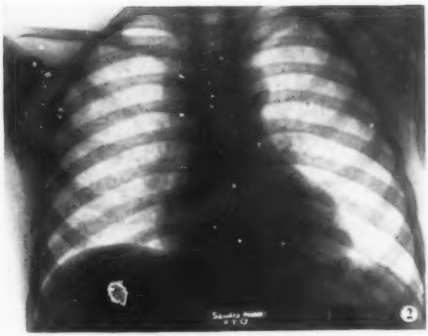
Reactivation of fibrocaseous tuberculosis was strikingly demonstrated in the Southern Greenland epidemic of measles in 1951, when 99·8 per cent. of the inhabitants of the district contracted measles (Christensen *et al.*, 1953). This included every case suffering from pulmonary tuberculosis. Deaths from tuberculosis and the number of new cases discovered rose significantly immediately after the epidemic. It was also confirmed that tuberculin allergy was suspended for eight to thirty-five days after the rash of measles.

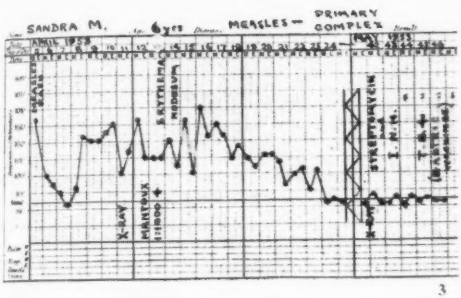
Empyema following measles appears to be largely an expression of uncontrolled secondary hæmolytic streptococcus infection. Even in pre-sulphonamide days it was quite rare in the very young children usually attacked by measles (2·2 per cent. of 232 cases of measles pneumonia in Ellison's material). Such young children are generally clinically resistant to streptococcal invasion. In these days empyema occurred frequently in older children and in adults (*e.g.* soldiers) attacked by measles. But with the use of antibiotics empyema following measles is now rare at all ages.

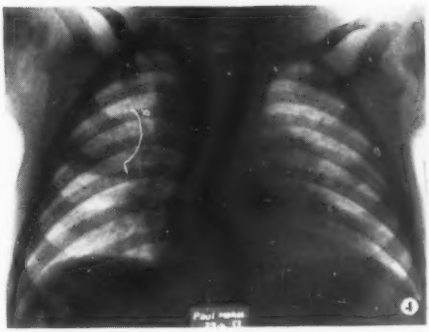
Myocarditis and Interstitial Pneumonia in Virus Infections

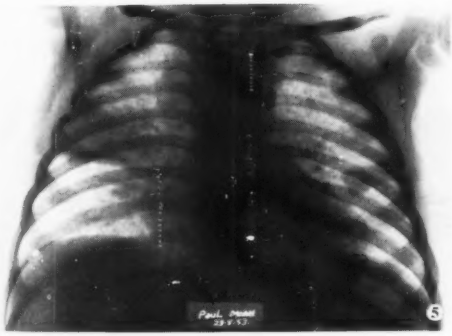
It is perhaps pertinent to draw attention here to the accumulating evidence that myocarditis is frequently present in nearly all acute virus infections. It has been demonstrated, for example, in measles, poliomyelitis, smallpox, mumps and rubella. In cases of smallpox in which secondary infection is











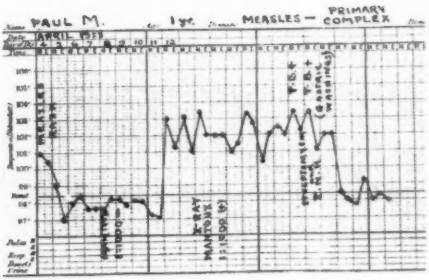


FIG. 1.—S.M. f. 6 years, Chest radiograph 6 days after Measles rash and 3 days after a secondary rise of temperature, shown later to be due to activated primary complex. Mantoux 1 : 1,000 positive, but not strongly, on 12th day of Measles (see chart Fig. 3).

FIG. 2.—Same case 4 weeks later, showing swollen hilar gland shadows. Pyrexia lasted 16 days and cleared spontaneously. T.B.+ once in gastric washings.

FIG. 3.—Same case. Temperature chart showing activated primary complex following immediately after measles.

FIG. 4.—P.M. 1 year, brother of S.M. Chest radiograph 14th day of Measles and 3rd day of secondary rise of temperature, which was shown later to be due to malignant primary complex. Mantoux 1 : 1,000 negative at this time, probably due to suppression of allergy by measles.

FIG. 5.—Same case 3½ weeks later. Malignant primary complex with hilar gland enlargement, upper lobe partial collapse, and miliary shadows.

FIG. 6.—Same case. Temperature chart showing activated malignant primary complex following about a week after the rash of measles.

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FIG. 7.—C.S., f. 5½ years, R. lateral chest in 7th week of whooping cough, showing collapse of middle lobe and parts of both lower lobes. The child was afebrile except for an occasional spike of temperature.

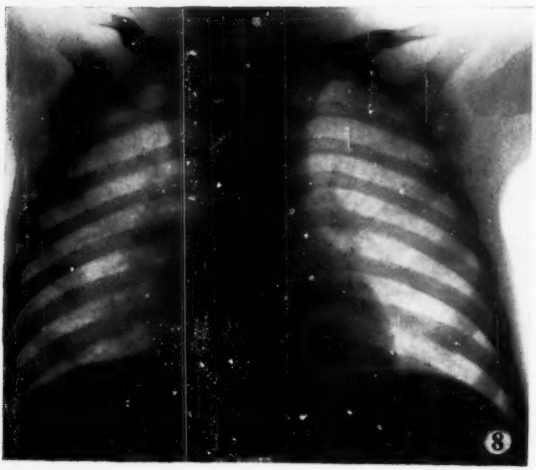

FIG. 8.—G.S., m. 3 years, whooping cough and activated primary complex with some miliary shadows. The temperature rose in the 4th week of whooping cough, and did not respond to penicillin or aureomycin. Mantoux 1 : 10,000 was negative, but 1 : 1,000 strongly positive. Streptomycin and I.N.H., given on the 11th day of the pyrexia, was followed by nearly normal temperature after 6 days. The miliary shadows were not seen until 2 weeks after chemotherapy began. There was a transitory rise of cells to 9 per cmm. in the spinal fluid.

controlled by antibiotics, it is now the chief cause of death, and in severe respiratory cases of poliomyelitis it is probably a factor in the production of cardiac failure. Jungeblut (1950) actually recovered the virus from the heart in fatal cases of poliomyelitis in man and experimental animals. Other authors have demonstrated the histological lesions of focal myocarditis in fatal cases of these infections (Larson, 1941; Saphir and Wyle, 1942). Systematic electrocardiographic examination of 71 children admitted with measles to the Willard Parker Hospital, New York, showed complete right bundle branch block in one case, $Q-T_e$ values above 0·430 second in 29 per cent. and prolonged P–R intervals in 30 per cent. All these abnormalities had not subsided by the time full activity is usually resumed after measles; the E.C.G. changes were more frequent in children under than over 8 years of age (Ross, 1952). Similarly an interstitial pneumonia, probably of virus origin, has been demonstrated, though rarely, in poliomyelitis (Saphir, 1945; Jurow and Dolgopol, 1953), chickenpox (Saslow *et al.*, 1953; Rosecan *et al.*, 1953) and in epidemic influenza. Any of these virus infectious diseases may therefore give rise occasionally to chronic myocardial and pulmonary sequelæ, although there is so far little proof of this.

Hæmolytic Streptococcal Infections

Pneumonitis and Carditis

Empyema and rheumatic heart disease are such obvious sequelæ of scarlet fever and streptococcal tonsillitis that they require no more than mention here. The rarer rheumatic pneumonitis and polyarteritis seem in most cases to be examples of streptococcal allergy, resulting from repeated infection in sensitised but non-immune subjects. The antigen-antibody reactions thus set up produce widespread lesions in mesodermal tissues. The basic lesion is a fibrinoid degeneration of collagen fibres, followed by infiltration with lymphocytes, mononuclears and giant cells (Aschoff nodule), and later by fibroblastic proliferation and fibrosis. These lesions are found in vessel walls and their surroundings, and especially in the endocardium, myocardium, pericardium and great vessels of the chest. They distort these structures and reduce local blood supply. Rheumatic pneumonitis may be partly due to vessel permeability produced in this way in the pulmonary interstitial tissues. Pericardial effusions, small pleural effusions, pulmonary fibrosis and even disseminated alveolar foci of ossification (Elkeles and Glynn, 1946) are possible, though relatively rare, chest sequelæ of streptococcal infections. Very similar chest lesions associated with rheumatoid arthritis have been described by Ellman (1947), Ellman and Ball (1948), and with juvenile rheumatoid arthritis by Leys and Swift (1949). In all such cases a worth-while investigation is estimation of the antistreptolysin O titre of the blood serum. In true acute rheumatism this is usually well above the normal figure of 1 in 150, although there are individual exceptions.

Diphtheria

Diphtheria is at present a relatively small problem in Great Britain but still a major one in many parts of the world. Chronic chest sequelæ are rare.

In recovered cases even severe myocarditis clears up remarkably and usually completely from the clinical point of view. But there are exceptions, especially in older subjects. A follow-up investigation of 210 cases who had shown clinical signs of heart disease during the acute stage of diphtheria revealed 1 case with marked disorder associated with alternating heart block, 2 cases who had subacute heart symptoms for several years, and 17 cases with well-marked E.C.G. abnormalities, including prolonged conduction time, complete heart block, bundle branch block, depression of ST, and changes in T waves in significant leads (Hoel and Berg, 1953). Bronchiectasis is also an occasional sequela of laryngeal, tracheal and bronchial diphtheria with its accompanying bronchopneumonia, judging by the frequency with which tracheotomy scars are seen in the necks of adult bronchiectatics (Lee Lander, 1950).

Poliomyelitis

Chronic Respiratory Deficiency

Recovered cases of respiratory poliomyelitis in which there has been some paralysis of intercostal muscles or diaphragm, or both, are usually left with some respiratory deficiency. The extreme case is the patient with the " frozen chest " and papery diaphragm, whose breathing is dependent chiefly upon the sternomastoids and other extraordinary muscles of respiration. His vital capacity may be as low as 500 c.c. and he is incapable of maintaining life without a respirator, except when completely at rest. Even then he may have to return to the respirator at intervals in order to rest his remaining muscles. Upper or lower respiratory infections will profoundly upset the respiratory balance and drive him at once back to some form of respirator and to a course of antibiotics. The atrophied diaphragm tends to permit gastric dilatation, and this may proceed to atony with continuous vomiting. If the tank respirator has to be used in such a gastric crisis the danger of inhalation of gastric contents becomes very grave. Continuous gastric suction and positive pressure pulmonary ventilation by means of a Beaver or other pneumoflator may, however, enable the patient to survive until the gastric crisis is over.

Many patients are left with lesser degrees of respiratory deficiency which do not prevent them from undergoing slight or moderate exertion. A breakdown is apt to occur, however, in the presence of acute respiratory infection. At such times these patients may require the use of a respirator for a few days as a matter of urgency. Those with only slightly deficient vital capacity usually develop very strong sternomastoids and serrati magni which enable them to maintain relatively normal respiration. Most of these respiratory cripples have some residual paralysis of arms and legs, often extensive, and usually require to be wheeled about in a chair, or to have a self-propelled or mechanical chair.

Histoplasmosis

Chest physicians may have on occasion to distinguish between scattered nodular infiltrates and calcifications in radiographs of the chest due to tuberculosis and those due to a benign form of histoplasmosis. Histoplasmosis is a fungus infection, restricted as far as is known to certain parts of the world,

chiefly the East Central part of U.S.A. near the junctions of Mississippi, Missouri and Ohio rivers, but also found in the south-eastern provinces of Canada, in Mexico, Central America, South America and South Africa (Mochi and Edwards, 1952). No definitely indigenous cases have yet been reported from Great Britain. The benign form of the diease may leave residua of calcified nodules not localised to the upper zones, but scattered throughout the lung fields. Many of these cases are tuberculin-negative and histoplasmin-positive skin reactors, but these skin tests cannot always be relied upon to distinguish between the two conditions (Edwards *et al.*, 1948). As a sequela of the infection of histoplasmosis, however, these scattered nodular calcifications should be borne in mind when the physician is dealing with cases from certain parts of the world.

Summary

1. Lobular, segmental or lobar collapse is a frequent accompaniment of the late form of bronchopneumonia in whooping cough. Small areas of collapse are also frequently found in ambulant cases not clearing up satisfactorily from the fourth week onwards. These are potential sources of bronchiectasis.

2. An attack of whooping cough concurrent with an unhealed tuberculous primary complex may cause the latter to flare up and become progressive.

3. The complications of measles are more easily controlled by antibiotics than those of whooping cough, and recent epidemics of measles are milder than formerly. Pulmonary collapse and bronchiectasis as sequelæ of measles are now accordingly comparatively rare.

4. A primary complex or any form of pulmonary tuberculosis concurrent with an attack of measles is very likely to be aggravated. In this respect measles is probably a greater potential danger than whooping cough.

5. Virus infections, such as measles, poliomyelitis, smallpox, mumps and rubella are often complicated by some degree of myocarditis, which may cause sequelæ.

6. Rheumatic heart disease is a frequent sequela, and pneumonitis and polyarteritis nodosa are rarer sequelæ of hæmolytic streptococcal infections.

7. Chronic myocardial disorder is an uncommon sequela of diphtheritic myocarditis.

8. Chronic respiratory deficiency and attacks of severe gastric dilatation are not uncommon sequelæ of respiratory poliomyelitis.

9. Diffuse calcified nodules in the lung fields may be residua of benign histoplasmosis contracted in certain parts of the world.

REFERENCES

Bentzon, Johanne W. (1953): *Tubercle*, **34**, 34.
Christensen, P. E., Schmidt, H., Bang, H. O., Anderson, Vera, Jordal, B., and Jensen, O. (1953): *Acta med. Scand.*, **144**, 450.
Edwards, Lydia, B., Lewis, J., and Palmer, C. E. (1948): *Publ. Hlth. Rep. Wash.*, **63**, 1569.
Elkeles, G., and Glynn, L. E. (1946): *J. Path. Bact.*, **58**, 517.
Ellison, J. B. (1931): *Arch. Dis. Child.*, **6**, 37.
Ellman, P. (1947): *Proc. Roy. Soc. Med.*, **40**, 332.
Ellman, P., and Ball, R. E. (1948): *Brit. Med. J.*, **2**, 816.
Hoel, J., and Berg, A. H. (1953): *Acta med. Scand.*, **145**, 393.

JUNGEBLUT, C. W. (1950): *J. Pediat.*, **37,** 109.
JUROW, S. S., and DOLGOPOL, VERA B. (1953): *Amer. J. med. Sci.*, **226,** 391.
KITCAT, C. DE W., and SELLORS, T. H. (1928): *Brit. Med. J.*, **1,** 1018.
LARSON, C. P. (1941): *Northwest Med.*, **40,** 448.
LEE LANDER, F. P. (1950): *Brit. Med. J.*, **2,** 1486.
LEYS, D. G., and SWIFT, P. N. (1949): *Ibid.*, **1,** 434.
MOCHI, A., and EDWARDS, PHYLLIS Q. (1952): *Bull. World Hlth. Org.*, **5,** 259.
OSWALD, N. (1947): *Proc. Roy. Soc. Med.*, **40,** 736.
ROSECAN, M., BAUMGARTEN, W. JR., and CHARLES, B. H. (1953): *Ann. Int. Med.*, **38,** 830.
ROSS, LUCILLE, J. (1952): *Amer. J. Dis, Child.*, **83,** 282.
SAPHIR, O. (1945): *Amer. J. Path.*, **21,** 99.
SAPHIR, O., and WYLE, S. A. (1942): *Amer. J. Med. Sci.*, **203,** 781.
SASLAW, S., PRIOR, J. A., and WISEMAN, B. K. (1953): *Arch. int. Med.*, **91,** 35.
WESTWATER, J. S. (1933): L.C.C. Ann. Rep.

SUPPURATIVE PNEUMONIA IN THE BANTU, ASSOCIATED WITH A MIXED BACTERIAL FLORA*

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Suppurative pneumonia was comprehensively defined by Nicholson (1950) as " an inflammatory consolidation of the lung which proceeds in whole or in part to suppuration." He stressed the importance of a heterogeneous group of bacteria in causing and maintaining suppuration, and named this variety *non-specific suppurative pneumonia* as opposed to the specific varieties due characteristically to particular organisms. Nicholson's concept embraces the conditions described as "chronic suppurative pneumonia" by Scadding (1938) and the migratory spread of suppurative pneumonia called " spreading suppurative pneumonitis " by Sellors (1946) and his colleagues.

The Present Study

The present study arose from a survey of all cases of pneumonia in adult Bantu patients admitted to the Pretoria General Hospital over a period of twelve months starting in September 1951. It was soon apparent that many of these patients were producing unusually large amounts of purulent sputum. They tended also to recover more slowly than the commoner cases of pneumonia and frequently developed cavitation of the lungs. In defining this group it was found practical to use Nicholson's criterion for " suppurative pneumonia " as comprising those cases in which more than 2 ounces of purulent sputum were produced in twenty-four hours. The remainder were regarded as cases of " non-suppurative " pneumonia. Most fell readily into one or other group and there were few border-line cases.

In all, 260 cases of pneumonia were studied. Nearly a quarter of the total (60 cases) was found to have suppurative pneumonia. Among the 60 cases, 1 was due to a partial bronchial obstruction caused by a bronchial carcinoma and 17 were caused by specific organisms. Among the latter were 6 cases of Friedländer pneumonia, 6 of staphylococcal pneumonia, 4 of pulmonary amœbiasis and 1 of pulmonary actinomycosis. Mixed growths of bacteria were obtained from the sputum of the remaining 42 cases. In 6 of these the primary cause was obvious: 3 arose by bronchogenic spread from infected bronchiectasis, 2 from secondary suppuration in tuberculous cavities and 1 from abscess formation in a pulmonary infarct.

None of these special types of suppurative pneumonia will be discussed here. The following analysis applies only to the remaining 36 cases, which conform in many respects to Nicholson's description of *non-specific suppurative*

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pneumonia. These cases were divided into two groups according to the radiological findings: those with lung abscess (27 cases) and those without (9 cases).

Clinical, Radiological and Bacteriological Findings

There were 30 *males* and 6 *females* in the present series, representing a preponderance of males in the ratio 5: 1. The *ages* of patients ranged from 14 to 80 years, the majority being between 20 and 40 years. Inhalation of a foreign body was not suspected in any case, nor were general anæsthesia or operations on the mouth, throat or elsewhere found to be a causative factor.

It was seldom possible to decide on clinical grounds whether cases were likely to show radiological signs of cavitation or not. *The onset of symptoms* in cases with lung abscess, however, was more frequently insidious. Only a half (13) began acutely. On the contrary, 8 of the 9 cases without cavitation had an acute onset. Two cases of lung abscess developed suddenly while the patients were in hospital, one following a diabetic coma and the other a series of epileptic seizures. The onset in both cases was marked by fever, pleuritic pain and the coughing of small quantities of foul sputum which soon increased in amount to several ounces per day. In each case a chest roentgenogram taken within two days of the onset showed obvious abscess formation. Two cases admitted within three days of becoming acutely ill with extreme pain in the chest, dyspnœa, fever and cough were found to have massive pyopneumothoraces. These cases will be discussed later in more detail. It was common for symptoms of lung abscess to develop gradually. Usually a cough occurred which was dry at first but was followed by the production of purulent sputum increasing in amount over a period of a few days.

Physical signs in the chest varied greatly. Cases with an abrupt onset usually had obvious signs of consolidation, but this was seldom found when the condition began insidiously. Most cases had merely a few crepitations in the affected areas of the lungs, and the classical signs of a pulmonary cavity were seldom encountered. In both cases of pyopneumothorax, however, the " anvil sound " and Hippocratic succussion could be clearly demonstrated.

Clubbing of the fingers occurred in 14 of the 27 cases of lung abscess and in 2 of 9 cases without cavitation. In 2 cases of lung abscess hypertrophic pulmonary osteoarthropathy was found in addition.

The quantity of *sputum* varied from 2 to 16 ounces in twenty-four hours, with an average of 6 ounces. It was frequently streaked with blood, but severe hæmoptysis did not occur. Fœtor was noted at some time in nearly all cases.

The initial *leucocyte count* in the cases with abscess varied between 7,000 and 24,000 per c.mm. In only 1 case was it higher than 20,000 per c.mm. In cases without cavitation the total count tended to be much higher and varied between 6,000 and 35,000 per c.mm. Four of the 9 cases showed counts over 20,000 per c.mm. The 2 cases with pyopneumonthorax had counts of 17,000 and 23,500 per c.mm. respectively.

Bronchoscopy was carried out in all cases. In none was an inhaled foreign body found, nor was there evidence of bronchial stenosis or intrabronchial neoplasm. All showed reddening of the mucosa of the bronchial orifice nearest

the lesion and of the adjacent mucosa in the main-stem bronchus. Considerable quantities of pus could be aspirated from lesions within reach of the sucker.

Radiologically there was either the appearance of cavitation with a variable amount of surrounding consolidation or a dense consolidation of one or more, usually adjacent, bronchopulmonary segments (Figs. 1A, 1B and 2).

In most of the cases with cavitation, healing was accompanied by the development of some bronchial distortion or bronchiectasis. This varied from a slight dilatation of the bronchial lumen to the formation of multiple, gross, cavity-like dilatations.

In 2 cases the suppurative process had spread to a fresh area of the lung at a stage when the primary lesion had almost healed. In one of these cases multiple small abscesses formed in the area of secondary spread, although there appeared to be no cavities in the original lesion (Figs. 3A and 3B). These cases conform to the description of "spreading suppurative pneumonitis" given by Sellors and his colleagues. The phenomenon is almost certainly due to bronchogenic spread of infection from one part of the lung to another.

Sputum Bacteriology. As noted already, a mixed bacterial flora was grown in all cases. The relative incidence of the various bacteria isolated is indicated in Table I.

TABLE I.—SPUTUM BACTERIOLOGY IN 35 OF 36 CASES OF SUPPURATIVE PNEUMONIA

(Figures indicate number of times organisms found.)

	26 *cases with lung abscess*	9 *cases without abscess formation*
S. viridans	17	5
Pneumococci	8	4
N. catarrhalis	7	2
Coliform bacilli	5	3
Diphtheroid bacilli	3	2
Hæmolytic streptococci	2	1
H. influenza	1	3
Fusiform bacilli and spirilla	2	1
Staphylococcus aureus	2	–
Non-hæmolytic streptococci	–	1

It is remarkable that there was no essential difference in the bacteriological findings whether abscess formation had occurred or not.

The sensitivity *in vitro* of 38 organisms isolated from the sputum of 24 cases is outlined in Table II. A modification of the " agar-cup " method described by Erlanson (1951) was used to determine the grades of sensitivity towards six commonly used antibiotics.

It is seen that about nine-tenths of the organisms tested were sensitive to ter mycin, chloramphenicol and aureomycin, whereas only about a tenth were markedly sensitive to penicillin, sulphathiazole and streptomycin.

Dental and Gingivival Sepsis.—Signs of infection in the mouth, pharynx, paranasal sinuses, ears and nose were carefully sought in all cases. Obvious signs of infection were found only in the gums and teeth. Dental and gingival sepsis were considered to be *absent* if there was no sign of infection whatever, or at most if only one or two small dental cavities were present, or if there

TABLE II.—SENSITIVITY IN VITRO OF 38 ORGANISMS ISOLATED FROM 24 CASES OF SUPPURATIVE PNEUMONIA

(The figures indicate the number of organisms tested.)

	Sensitive	*Moderately sensitive*	*Insensitive*
Terramycin	26	9	3
Chloramphenicol ..	21	13	4
Aureomycin	17	16	5
Streptomycin	6	24	8
Penicillin	5	17	16
Sulphathiazole ..	4	15	19

was no more than a thin zone of hyperæmia around the gum margins. Dental and gingival sepsis were considered to be *present* if caries and gum infection in excess of the above were noted. The difference between the two groups was usually so gross as to be unmistakable. Most cases with sepsis had extensive caries and massive tartar encrustations together with swollen suppurating gums. The 200 cases of *non-suppurative* pneumonia were used as a control group for assessing the significance of dental sepsis. Cases of suppurative pneumonia with and without pulmonary cavitation were considered together and the observations are analysed in Tables III and IV.

It is seen from the tables that the two groups of cases are comparable in respect of age distribution. There is a significant preponderance of dental

TABLE III.—INCIDENCE OF DENTAL CARIES AND/OR GINGIVAL SEPSIS IN 36 CASES OF SUPPURATIVE PNEUMONIA

Age group	*No of cases in each age group*	*No. of cases with sepsis*
11-20 years	3	1
21-30 ,, ...	12	10
31-40 ,, ...	11	9
41-50 ,, ...	5	5
51-60 ,, ...	3	3
61-70 ,, ...	1	1
71-80 ,, ...	1	
Total cases	36	30 (83%)

TABLE IV.—INCIDENCE OF DENTAL CARIES AND/OR GINGIVAL SEPSIS IN CONTROL GROUP OF 200 CASES OF NON-SUPPURATIVE PNEUMONIA

Age group	*No. of cases in each age group*	*No. of cases with sepsis*
11-20 years	34	1
21-30 ,, ...	73	4
31-40 ,, ...	58	12
41-50 ,, ...	21	11
51-60 ,, ...	8	5
61-70 ,, ...	6	3
Total cases	200	36 (18%)

sepsis in the suppurative pneumonia group. It is also apparent, though not unexpected, that the number of cases with dental sepsis increases with age in both the observed and control groups.

Site of Original Pulmonary Lesion.—In 2 of the 9 cases without cavitation multiple segments were already involved at the time of admission to hospital, and in 2 cases with pyopneumothorax the original lesion could not be placed. In the remaining cases the sites of the original lesions are indicated in Table V.

TABLE V.—SITE OF ORIGINAL LESION IN 32 OF 36 CASES OF SUPPURATIVE PNEUMONIA

	Cases with lung abscess	*Cases without abscess formation*
No. of cases with lesions of—		
Posterior segment right upper lobe ..	19	5
Posterior segment left upper lobe ..	2	–
Apical segment right lower lobe	2	2
Anterior segment right upper lobe ..	1	–
Medial basal segment right lower lobe ..	1	–
Total cases	25	7

The site of the lesion was essentially similar whether abscess formation had occurred or not. It is noteworthy that the posterior segment of the upper lobe or apical segment of the lower lobe was involved in 30 of 32 cases, and that the right lung was involved 15 times more often than the left. In cases without cavitation in which the posterior segment of the upper lobe had been involved the consolidation in most cases also involved the axillary portion of the anterior segment.

CONCEPT OF PATHOGENESIS

A critical consideration of the findings in the present series of cases shows that the aspiration of infected material from the mouth must have precipitated the pulmonary infection in most of the patients studied. This may be deduced from a consideration of the sputum bacteriology, incidence of dental sepsis and the site of the primary lesion. Each of these features will now be considered in detail.

The *mixed bacterial floras* isolated in this series of cases are composed of organisms frequently found in infections of the mouth and pharynx. Ramsay and Scadding (1939) suggested that certain lung infections with transient radiological signs were due to inhalation of infected mucus from the upper respiratory tract. Their cases, however, showed relatively mild catarrhal infections with no gross sepsis. Nicholson (1950) extended this thesis to cases of suppurative pneumonia. He was able to find a likely source of aspirated material in most of his cases, but the incidence of dental sepsis was only 25 per cent. He did not say whether this figure was higher than that for the general population. Brock (1947) gave the incidence of dental sepsis in a large series of cases of lung abscess as 19 per cent., but the comparative incidence in the general population or a suitable control group was again not stated.

In a particularly careful study, Stern (1936) noted an incidence of gross

dental sepsis in 84 per cent. of a series of 115 cases of lung abscess, as compared with 12 per cent. and 14 per cent. in two control groups. Recently Wig (1951) found dental sepsis in 14 of 16 cases of lung abscess where no other cause was apparent. There is a close correlation of the figures of the present series (83 per cent. with dental sepsis as compared with 18 per cent. in the control group) with those of Stern.

The *situation of the primary lesion* in the present series supports further the hypothesis of aspiration. Brock (1942) and his co-workers showed that iodised oil instilled into the trachea lodged in the posterior segment of the upper lobe if the patient lay on his side and in the apex of the lower lobe if he lay on his back. This occurred for purely anatomical reasons through the influence of gravity. In 30 of 32 cases in the present series the primary lesion is significantly situated in precisely these areas.

It is postulated therefore that suppurative pneumonia with a mixed bacterial flora is due in nearly all cases in the Bantu to aspiration of infected material from the teeth and gums. It is probable that this occurs during sleep when the cough reflex is relatively depressed. Right-sided lesions may preponderate because the right main bronchus continues more directly from the trachea than the left, or it may be related to the posture of the patient at the time of aspiration. The sleeping posture of patients was shown by Helm (1951) to be important in determining the bronchogenic spread of infection in pulmonary tuberculosis. It may also be important in fixing the site of the lesion in suppurative pneumonia of the type under discussion.

The pathogenesis of 6 cases without dental sepsis, of which three had small but obvious lung abscesses, remains to be discussed. One became ill in hospital shortly after recovering from diabetic coma; it is probable that secretions aspirated from the mouth or pharynx during coma were responsible for the lung lesion. Another case followed alcoholic stupor and a similar mechanism appeared likely. In 2 further cases there were moderate tartar encrustations on the teeth and the gum margins were hyperæmic. The 2 remaining patients had been ill with an influenza-like illness and cough for one and three weeks respectively, before suddenly developing pain in the chest and producing considerable quantities of purulent sputum. It seems likely that they had inhaled infected mucus during the course of an upper respiratory infection. It is perhaps significant that all these cases recovered completely with conservative medical treatment. This may indicate that a relatively mild suppurative pneumonia can result from inhalation of slightly infected mucus, as opposed to the inhalation of grossly infected pus or tartar which probably takes place in the majority of cases. The pathogenesis, therefore, appears to be intermediate between that of the more usual type of " non-specific suppurative pneumonia " and Scadding's " benign aspiration pneumonia."

Complications

Apart from bronchogenic spread of infection and residual bronchiectasis, the only serious complication was *putrid empyema.*

Two acutely ill patients, admitted to hospital within three days of the onset of their illness, were found to have massive pyopneumothoraces. The

average intrapleural pressure was 8 and 10 cm. of water above atmospheric pressure respectively in the 2 cases. In neither could a bronchopleural fistula be demonstrated. The underlying lung was compressed and no obvious signs of lung disease could be seen on the roentgenograms (Fig. 6). Bronchoscopy and bronchography were equally uninformative. More than 2 litres of thin foul-smelling pus were removed from the pleural cavity at the first aspiration in each case. Culture of the pus yielded a mixed growth of *S. viridans*, hæmolytic streptococci, *N. catarrhalis*, spirilla and fusiform bacilli. Treatment consisted of complete aspiration of pus daily and intrapleural instillation of penicillin and streptokinase, together with parenteral penicillin and oral sulphadiazine. Later, when the results of the *in vitro* sensitivity tests became known, terramycin was given. The empyemas soon became sterile and the fluid turned a clear straw colour. In both instances, however, the lungs failed to expand and decortication operations were successfully performed.

It is believed that these lesions were due to the rupture into the free pleural space of a small, fulminating, subpleural abscess with the formation of a tension pyopneumothorax. The perforations must have been minute and probably closed rapidly. An almost identical but fatal case of pyopneumothorax in a 42-year-old Bantu male is described in the hospital autopsy records. A small subpleural abscess, 2 cm. in diameter, situated in the apex of the right lower lobe and without any apparent surrounding consolidation of the lung, was found to have ruptured into the pleural space, resulting in a massive putrid pyopneumothorax. Two further cases of the same type have been seen since the completion of this study, suggesting that this complication is not uncommon in the Bantu.

Treatment, Course and Prognosis

Penicillin and sulphadiazine were administered and postural drainage was employed in all cases as soon as the site of the lesion was determined. Bronchoscopy was carried out and as much as possible of the infected secretions sucked out by means of a rubber-tipped sucker. Four cases of lung abscess were observed to improve markedly after bronchoscopy with aspiration, and in 3 the abscesses healed completely in a matter of days. As soon as the results of the bacterial sensitivity tests *in vitro* became known the appropriate antibiotic was given. The findings shown in Table II suggest that the results may have been improved if one of the newer antibiotics had been given from the start.

In most cases without cavitation pyrexia lasted for three to fifteen days with an average of eight days. All cases recovered completely, except one who developed bronchiectatic changes in the affected pulmonary segments. Cases with bronchogenic spread of infection tended to have prolonged pyrexia. One case of "spreading suppurative pneumonitis" exhibited fever with clinical and radiological signs of a lung infection for more than two months despite the administration of appropriate antibiotics.

Pyrexia varied considerably in cases with lung abscess and several showed no pyrexia at all. Of the 27 cases, 1 was fatal. This patient was extremely weak and emaciated on admission. He died within two days. Of the re-

maining 26 cases, 13 recovered completely with conservative medical treatment. In view of the serious consequences of chronic lung abscess, lobectomy was advised in all cases with cavitation which persisted longer than six weeks. Eight patients felt so well when the acute infection was over that they refused operation. There was no radiological evidence of healing of the chronic abscesses in these cases during the following three months. They were not readmitted to hospital during the next year nor did they report at the out-patients department. In 3 cases a lobectomy was done and in 2 cases with an inexpandable lung following pyopneumothorax decortication was performed (Prof. J. K. Bremer).

Illustrative Case Reports

(1) *Suppurative pneumonia without abscess formation.* The patient was a 30-year-old Zulu male. Three days before admission he suddenly developed a pleuritic pain in the right axilla, felt feverish and coughed up increasing quantities of blood-stained sputum. His temperature on admission was 101° F., pulse 130 and respirations 50 per minute. On examination *herpes labialis*, grossly infected gums, carious teeth and signs of consolidation of the right upper lobe were found. A roentgenogram of the chest showed a dense consolidation of the posterior segment and axillary portion of the anterior segment of the right upper lobe (Figs. 1A and 1B). Four ounces of viscid, blood-stained, purulent sputum were produced in twenty-four hours. It was found on direct examination to contain spirilla, fusiform bacilli and numerous cocci. Culture yielded a profuse growth of *Streptococcus viridans* together with scattered colonies of pneumococci and diphtheroid bacilli. The patient was treated with penicillin and sulphadiazine and made a rapid and uneventful recovery. A bronchogram two weeks later showed no bronchial distortion.

(2) *Suppurative pneumonia with abscess formation.* The patient was a 28-year-old Msutu male. Two months before admission to hospital he had developed a dry cough. A few days later he experienced a severe pain in the left axilla. Simultaneously he coughed up small quantities of fœtid, purulent sputum which rapidly increased in amount and was sometimes streaked with blood. After a month his fingers, fore-arms and ankles became painful and swollen. On examination he was found to have marked clubbing of his fingers and thickening of the wrists and ankles. There was gross gingival sepsis and signs of cavitation of the left upper lobe. A roentgenogram of the chest showed two large abscess cavities with fluid levels in the posterior segment of the left upper lobe (Fig. 2). Roentgenograms of the wrists and ankles showed periosteal thickening of the radius, ulna, tibia and fibula (hypertrophic pulmonary osteoarthropathy). Six ounces of foul-smelling purulent sputum were produced in twenty-four hours from which a mixed culture of *S. viridans* and *N. catarrhalis* was grown. Bronchoscopy revealed reddening of the left upper lobe orifice and pus in the left main bronchi. The abscesses persisted despite intensive treatment with penicillin, sulphadiazine and terramycin. Lobectomy was successfully performed. A post-operative empyema and bronchopleural fistula healed spontaneously and uneventfully.

(3) *So-called "spreading suppurative pneumonitis."* The patient was a 35-year-old Msutu male, who had been ill for three days with pain in the chest and cough. He was found to have marked dental sepsis and consolidation of the posterior segment and axillary portion of the anterior segment of the right

upper lobe. Three ounces of purulent sputum were produced in twenty-four hours which on culture yielded a mixed growth of *S. viridans*, *N. catarrhalis* and *H. influenzæ*. The patient was treated with penicillin and sulphadiazine and appeared after ten days to have recovered completely. At this stage cough again became troublesome, his temperature rose to 102° F., and the sputum increased to 5 ounces in 24 hours. A chest roentgenogram fourteen days after admission to hospital showed almost complete clearing of the original lesion, but consolidation with multiple small abscesses had developed in the left upper lobe and lingula (Figs. 3A and 3B). This lesion healed slowly after ten weeks, leaving a moderate degree of pulmonary fibrosis and slight bronchial distortion.

(4) *Putrid pyopneumothorax*. The patient, a 28-year-old Msutu male, appeared on admission to hospital to be dying. Relatives stated that he had complained of a sudden pain on the right side of the chest, extreme breathlessness and a feeling of chilliness two days before admission. On examination his pulse was feeble and the rate 130 per minute. His blood pressure was 80/50 mm. Hg. He was dyspnœic and cyanosed. There were signs of hydropneumothorax. A roentgenogram of the chest (Fig. 4) showed a large hydropneumothorax on the right and a normal left lung. The intrapleural pressure was 8 cm. of water above atmospheric pressure. Large quantities of thin, brown, offensive pus were aspirated daily. It was found to contain spirilla, fusiform bacilli, hæmolytic streptococci and *N. catarrhalis*. No bronchopleural fistula could be demonstrated. The patient's condition improved rapidly. Although the empyema became sterile soon after intrapleural penicillin injections were commenced, the lung failed to expand. A decortication operation was then successfully performed.

Discussion

The most important observation in the present series is the demonstration of the rôle of dental sepsis in the pathogenesis of suppurative pneumonia of the "non-specific" type. In most cases this type proved to be a form of aspiration pneumonia due to inhalation of infected material from the teeth and gums.

Although the present study refers only to the Bantu, there is no reason to believe that the conclusions do not apply equally to Europeans. Dental neglect and lack of adequate dental care are so much commoner in the Bantu that the results of dental sepsis are more easily and convincingly demonstrated in this race. There is a striking similarity between the incidence of dental sepsis recorded by Stern and that of the present series, although the groups of cases studied are not strictly comparable.

The differing etiology in suppurative and non-suppurative pneumonias is borne out by the sharp difference in the incidence of dental sepsis. It is likely, nevertheless, that a differentiation based upon the amount and character of the sputum produced will cause some of the milder types of aspiration pneumonia to be included in the group of non-suppurative pneumonia.

Cases of suppurative pneumonia without dental sepsis can frequently be traced to inhalation of infected mucus from the mouth or pharynx. These pneumonias appear to be relatively mild, though more virulent than the "benign aspiration pneumonia" described by Scadding.

Special consideration of the sputum bacteriology, site of the lesion and

incidence of dental sepsis indicates that cases with and without cavitation probably have a common pathogenesis. The actual factors which determine abscess formation are open to speculation. It may depend on the virulence of the infecting organisms, on the local or general resistance of the host or other undetermined factors.

Particularly virulent infections, if situated close to the periphery of the lung, rapidly perforate the pleura, giving rise to a putrid pyopneumothorax. Complications of this nature appear to be quite frequent in the Bantu.

Better dental services and a greater appreciation of the benefits of dental hygiene among the Bantu will almost certainly lower the morbidity from suppurative pneumonia of this type.

Other well-known types of aspiration pneumonia, such as those occurring after tonsillectomy and other operations and following inhalation of foreign bodies, undoubtedly occur in the Bantu, but they must be considered rare.

Summary

During a study of 260 cases of pneumonia in the Bantu nearly a quarter of the cases were found to have a suppurative pneumonia. About a third of these were due to specific bacteria and the remaining two-thirds to a mixture of non-specific bacteria.

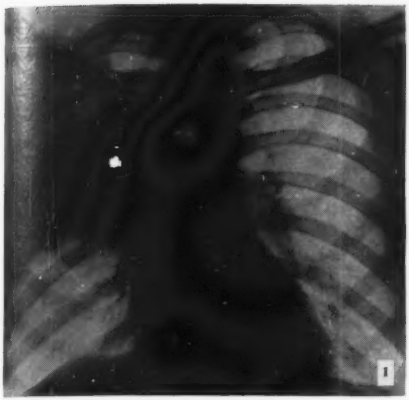
A critical analysis of the sputum bacteriology, site of the original pulmonary lesion and incidence of dental sepsis in cases not due to single specific bacteria, indicates that most of these cases were caused by the aspiration of infected material from carious teeth or septic gums. There seems to be no essential difference in etiology between cases with or without abscess formation.

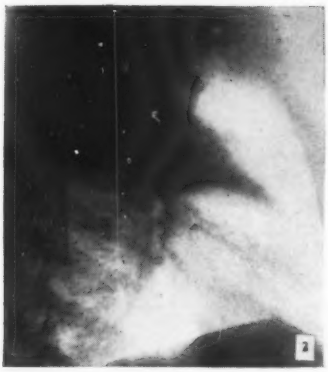
It is suggested that various grades of severity of the condition may be recognised. The mildest form occurs independently of dental sepsis but may give rise to abscess formation; a more virulent form gives rise to rapid extensive destruction of lung tissue with cavitation. A fulminating form occurs in which a subpleural lesion rapidly perforates the parietal pleura, causing a putrid pyopneumothorax; this is the most important complication noted.

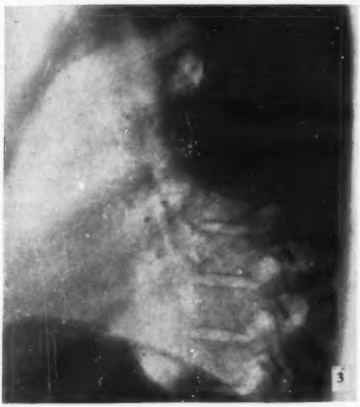
Improved dental services can probably reduce the morbidity from suppurative pneumonia.

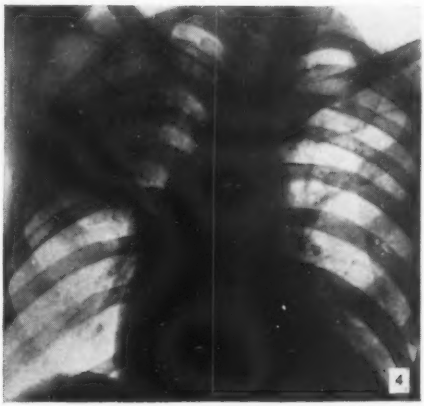
References

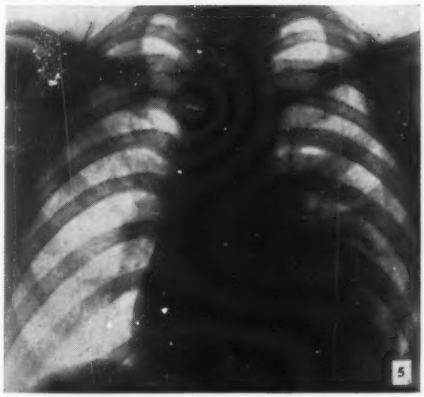
Brock, R. C. (1947): *Guy's Hosp. Rep.*, **96,** 141.
Brock, R. C., Hodgkiss, F., and Jones, H. O. (1942): *Ibid.*, **91,** 131.
Erlanson, P. (1951): *Acta Path. Microbiol. Scandinav.*, Supp. 58.
Helm, W. H. (1951): *Thorax*, **6,** 417.
Nicholson, H. (1950): *Lancet*, **2,** 549, 605.
Ramsay, H., and Scadding, J. G. (1939): *Quart. J. Med.*, **8,** 79.
Scadding, J. G. (1938): *Proc. Roy. Soc. Med.*, **31,** 1259.
Sellors, T. H., Blair, L. G., Houghton, L. E., Thompson, V. C., and Pryce, D. M. (1946): *Thorax*, **1,** 146.
Stern, L. (1936): *J. Thorac. Surg.*, **6,** 202.
Wig, K. L. (1951): *Indian J. Med. Sci.*, **5,** 529.

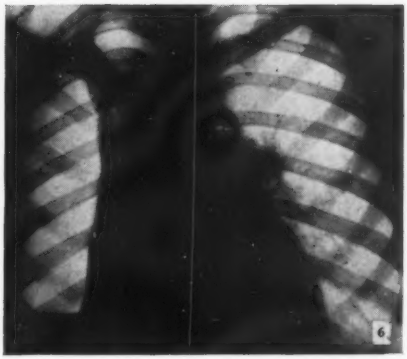












FIGS. 1 and 2.—(P.A. and right lateral films.) Suppurative pneumonia without abscess formation. There is dense consolidation of the posterior segment and of the axillary portion of the anterior segment of the right upper lobe.

FIG. 3.—Suppurative pneumonia with abscess formation. There is a large abscess with a fluid level situated in the posterior segment of the left upper lobe.

FIGS. 4 and 5.—"Spreading suppurative pneumonitis." The first roentgenogram shows consolidation of the posterior segment of the right upper lobe. The second, taken two weeks later, shows almost complete healing of the original lesion. At this stage, however, consolidation of the left upper lobe and lingula had developed together with multiple small abscess cavities.

FIG. 6.—Putrid pyopneumothorax. There is a large pyopneumothorax on the right with compression of the underlying lung.

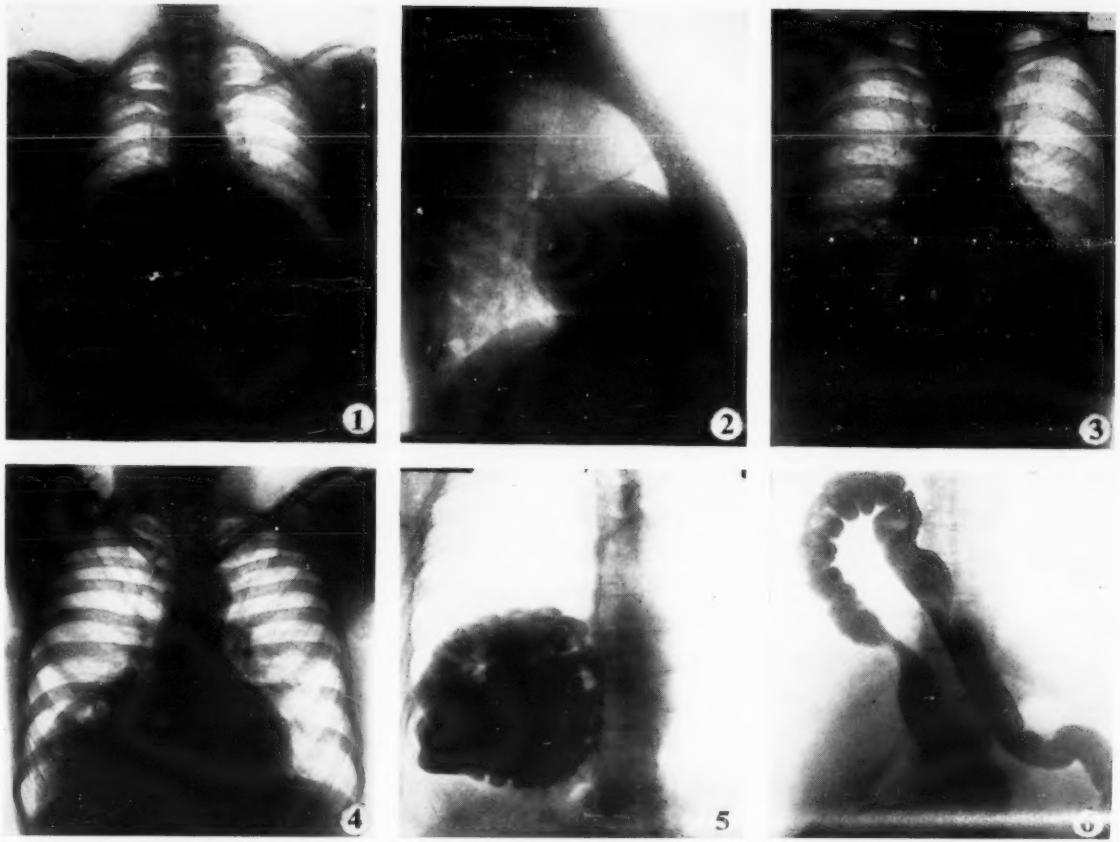


FIG. 1 and FIG. 2.—Characteristic appearances of Foramen of Morgagni hernia (Case 4).

FIG. 3.—Liver hernia—note air space on medial side.

FIG. 4 and FIG. 5.—Hernia containing bowel. Note small gas shadow compared with mass of bowel in hernia (Case 5).

FIG. 6.—Barium enema on Case 4. Note constriction of bowel entering sac.

SUBCOSTOSTERNAL (FORAMEN OF MORGAGNI) DIAPHRAGMATIC HERNIA

By G. Cruickshank, P. P. Goel and M. E. M. Macedo

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Hernia through the foramen of Morgagni is one of the least common types of diaphragmatic hernia. Harrington (1951) in 534 diaphragmatic hernias encountered only 14 of the subcostosternal type. Warwick Brown (1952) states that less than 3 per cent. of all diaphragmatic hernias are of this type.

The purpose of the present paper is to report six cases of this entity seen and treated in the Leicester Chest Unit and to emphasise certain points of diagnostic and therapeutic importance.

Case Reports

Case 1. Male, aged 53. History of shortness of breath for one year with slight difficulty in swallowing. X-ray showed a grapefruit-sized shadow placed anteriorly and medially in the right chest immediately above the diaphragm. A pre-operative diagnosis of mediastinal lipoma was made. At right thoracotomy a typical hernia through the foramen of Morgagni was found. The sac contained mainly omentum. The hernial orifice was closed with considerable difficulty.

Case 2. Male, aged 38. History was of odd subcostal pain unrelated to meals for two years. The X-ray showed a typical right-sided Morgagni hernia containing bowel. This was repaired by the abdominal route without difficulty.

Case 3. Male, aged 51. This man complained of some indigestion and upper abdominal pain. Radiologically there was an opacity typical of a right-sided Morgagni hernia. A diagnostic pneumoperitoneum confirmed the diagnosis. The hernia was repaired by the abdominal route. The sac contained omentum and the foramen of Morgagni admitted only two fingers.

Case 4. Female, aged 42. A Mass Radiography pickup. History of winter cough and some dyspnœa was elicited, but no abdominal symptoms. Radiologically a large right-sided Morgagni hernia was demonstrated. Barium enema showed a loop of transverse colon entering the sac. The hernia was repaired by the abdominal route without difficulty (Figs. 1, 2 and 6).

Case 5. Male, aged 44. A Mass Radiography pickup. On questioning this man complained of a feeling of choking and suffocation when lying on his right side (the side of the hernia). Plain X-ray showed a large Morgagni hernia with a small amount of gas in it. Barium enema showed the majority of the large bowel to be in the chest. The hernia was repaired by the abdominal route. The sac contained most of the large bowel and a part of the terminal ileum. This is considered to be a simple Morgagni hernia associated with malrotation of the gut (Figs. 4 and 5).

Case 6. Male, aged 58. This man complained of some right-sided chest

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pain and dyspnœa. Radiologically a small Morgagni hernia was shown which was considered to contain only omentum. A barium enema showed the transverse colon to be abnormally high in position. The hernia was repaired by the abdominal approach without difficulty.

Etiology and Surgical Anatomy

The typical foramen of Morgagni hernia is almost certainly congenital in origin, although, unlike most other congenital diaphragmatic hernias, a sac is always present. However, herniation through the foramen of Morgagni without a sac has been met with. Proof of an embryological background is not easy. Harrington (1951) states: " It is impossible to explain these occurrences on a basis of faulty fusion or improper disposition of the embryonic mesodermic elements which go to form the diaphragm, as the anterior portion of the diaphragm is derived from the septum transversum only. But the consistency of the location of the hernial opening, the fairly constant relationship of the neck of the sac to the round and falciform ligament of the liver, and the frequency of right-sided hernia, as well as associated non-rotation of the right portion of the colon, all strongly suggest a fundamental embryological basis for these hernias."

A subcostosternal hernia is, in fact, a direct hernia through a congenital defect due to faulty attachment of the diaphragm to the costal cartilages and xiphisternum. Normally in this situation there is only a natural space—the space of Larrey or foramen of Morgagni—occupied by the epigastric vessels which will eventually anastomose with the internal mammary vessels. These openings, one on either side, are filled with areolar tissue and covered above by pleura and below by peritoneum.

The defect found at operation in these cases is typically ovoid, lies immediately to one side of the midline (usually the right), the costal cartilages forming its anterior rim and the diaphragm its posterior. The falciform ligament of the liver lies generally to the left of the defect, although in case 4, a right-sided hernia, it lay to the right of the opening.

The contents of the sac vary, but generally consist of omentum alone or omentum with large bowel. In one of our cases the majority of the large bowel lay in the sac, together with the appendix and terminal ileum.

Clinical Manifestations

We wish here to emphasise that many of these hernias are virtually symptomless, and that when symptoms do occur they are likely to take the form of dyspnœa and chest pain rather than to be referable to the alimentary tract. For these reasons, many of these hernias are first seen either in Mass Radiography Units or by Chest Physicians and are very frequently diagnosed as having an intrathoracic origin. For example, such diagnoses as " mediastinal cyst," " hydatid cyst," had been made in our cases before we saw them. This state of affairs is in complete contradiction to hernias through the œsophageal hiatus, whose symptoms are pre-eminently alimentary.

The symptomatology in our own cases varied from the completely symptomless to some who complained of dyspnœa and chest pain, with occasional

abdominal colic. One man, who had most of his large bowel in the sac, complained of dyspnœa and choking sensations only when lying on the side of the hernia. Undoubtedly the symptoms vary with the contents of the hernia, but from our own experience we cannot agree with Harrington, who states that where bowel is contained in the sac the symptoms are primarily abdominal.

Radiological Appearances

(*a*) *Plain Films:* These are very typical (Figs. 1 and 2)—there is a rounded shadow in the costophrenic angle situated immediately beneath the sternum in the lateral view, having a very characteristic shape in lateral projections. No lung can be seen between the shadow and the heart border in the P.A. film (Fig. 3). The lateral film shows characteristically an acute angle between the posterior edge of the hernial shadow and the diaphragm, a point which may aid in differentiating it from a herniation of the liver, in which this angle is well " rounded-off " or non-existent. Gas containing areas indicating the presence of bowel in the sac may be seen, although their absence cannot be taken as evidence to the contrary—the gas may be obscured by the presence of large amounts of omentum within the sac (Figs. 4 and 5).

(*b*) Confirmation of the diagnosis may be obtained by *barium enema* which will demonstrate large bowel within the sac (Fig. 6), or in purely omental hernias will show an upward and forward displacement of the transverse colon. It has been our experience that a barium meal is of little value in confirming the presence of this type of hernia. In one case the diagnosis was missed elsewhere because it was assumed that a negative barium meal excluded diaphragmatic hernia completely.

(*c*) Diagnostic pneumoperitoneum may on occasion be a valuable method of confirming the diagnosis, particularly where confusion exists between a liver hernia and an omental hernia. Air below the diaphragm will demonstrate the differing shape of the " sacs " in the two types—in the case of a liver hernia it is likely that the liver will fall away completely from the diaphragm, while in a Morgagni hernia it is most unlikely that the contents of the sac will reduce themselves, owing to the relatively narrow neck of the sac.

Differential Diagnosis

The commonest source of diagnostic error is lack of familiarity with the characteristic radiological features of the condition. However, difficulty may be encountered in deciding between an intrathoracic tumour or cyst and a protrusion of the abdominal contents into the chest. A diagnostic pneumoperitoneum will resolve this doubt. It remains to differentiate a subcostosternal hernia from a liver hernia—as has already been indicated there are radiological methods which should resolve this doubt in most cases.

Failure to differentiate between a subcostosternal hernia and an intrathoracic cyst may mean that if exploration is undertaken the chest will be opened instead of the abdomen. This was done in the first case in this series and great difficulty experienced in dealing adequately with the hernia which was found. The abdominal approach is undoubtedly mandatory for this type of hernia if a satisfactory operation is to be carried out.

Treatment

The only satisfactory treatment for this type of hernia is surgical, even though only omentum be present in the sac. It seems inevitable that the sac will increase in size with the passage of time, and that eventually bowel will enter it, with attendant risk of intestinal obstruction.

Operation is simple, safe and satisfactory, and in our opinion should be carried out except where adverse factors (such as old age) obtain.

The approach should be an abdominal one, through a right upper paramedian incision carried right up to the costal margin. The contents of the sac are generally reduced with ease, the sac inverted and excised, and finally the freshened edges of the defect brought together with a series of interrupted silk sutures—lack of diaphragm in the anterior part of the defect can easily be overcome by suturing the posterior margin of the defect to the costal margin and rectus sheath. In only one of our cases was any difficulty encountered in closing the defect adequately—this was the patient on whom because of a diagnostic error a thoracotomy was performed. Post-operative progress has been completely uneventful in all cases. There has been no recurrence of the hernia in any patient. Those patients having symptoms referable to the hernia have been completely relieved.

Summary

1. Six cases of subcostosternal diaphragmatic hernia are reported.
2. Stress is laid on the fact that these hernias are seen either as symptomless Mass Radiography pick-ups, or because of respiratory symptoms.
3. The typical radiological appearances are described.
4. Treatment is surgical—the abdominal route should be employed.

References

Clay, R. C., and Hanlon, C. R. (1951): *J. Thor. Surg.*, **21**, 57.
Meyer, H. W. (1950): *J. Thor. Surg.*, **20**, 235.
Harrington, S. W. (1951): *Rev. Gastroenterology*, **18**, 243.
Warwick Brown, R. (1952): *Thorax*, **7**, 266.

PITCH AND PULMONARY CARCINOMA

By Ian Lodge Patch

From the London Hospital

Although epithelioma resulting from occupational exposure to pitch, tar and related compounds is a commonplace (Pott, 1775; Volkmann, 1876; O'Donovan, 1920), information concerning the effect of these substances on the lung in man is scanty. Standard accounts of pulmonary carcinoma sometimes include them as a possible cause (Macrae, Funk and Jackson, 1927; Heller, 1950; Hueper, 1950, 1952; Graham, 1941; Perry, 1952), although other and earlier authorities regarded the evidence as inconclusive (Rubin, 1947; Davidson, 1948; Norris and Landis, 1938).

In 1916 Yamagiwa and Ichikawa established the carcinogenicity of tar experimentally, and Passey provided a similar proof for soot in 1922. When the rise in incidence of lung carcinoma was observed about 1925 (Kikuth, 1925; Young and Russell, 1925; Katz, 1927; Macrae *et al.*, 1927) the presence of such suspicious substances in the urban atmosphere was frequently cited in explanation of the increase. There is little to support this general relationship, which is now discredited. Even Campbell's demonstration (1934, 1937, 1939) that mice exposed to road dust containing 2 per cent. of tar frequently showed that pulmonary carcinomata is of doubtful relevance to man. Kennaway and Kennaway (1936) pointed out that in any case road dust was a negligible source of atmospheric tar for town-dwellers exposed for many earlier decades to the soot of domestic fuel containing as much as 40 per cent. of tar (Cohen and Ruston, 1925). Such factors as these are assumed to explain the higher incidence of pulmonary carcinoma in the urban population. Assessment of the possible agents involved is further complicated by tobacco smoking, only recently established as an important factor in the development of bronchial carcinoma (Doll and Bradford Hill, 1952).

Of the carcinogens long known to exist in coal-tar 3 : 4 benzpyrene was the first identified (Haddow and Kon, 1947), but subsequent work (Berenblum and Schoental, 1947; Kling, Samssonow and Heros, 1938a, 1938b) has shown that tar fractions free from 3 : 4 benzpyrene are also carcinogenic, and must contain several active substances as yet unknown. For the purposes of this review, therefore, no distinction is made between tar (a viscous liquid originating in the thermal decomposition of organic materials—Bunbury, 1950), pitch (the residuum left after distillation of tar) and soot (the particulate product of the incomplete combustion of organic carbonaceous material), all of whose carcinogenicity is well recognised.

The validity of these substances as causes of pulmonary carcinoma in man might be established in several ways:

1. By a statistical survey of causes of death in all workers with the suspected substances.

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2. By a radiological survey of the chests of such workers.
3. By an occupational analysis of many fatal cases of carcinoma of the lung.
4. By report of individual cases in which the cause of the neoplasm was suggested by the circumstances of its origin.

In addition, experimental evidence might be adduced.

It is appreciated that a solitary case, such as the present, establishes nothing and that its suggestive circumstances only indicate a possible field for further research.

Case Report

J. McD., aged 41, was admitted to the London Hospital on June 28, 1952, under Dr. Kenneth Perry. In 1925, aged 14, he started work in the plastics industry, mixing in heated drums asbestos, slate powder and pitch or bitumen in varying proportions. The drums emitted much fume and there was no exhaust ventilation. Intermittently he wore a simple gauze respirator, never for longer than two hours daily. In 1935, after ten uninterrupted years, he changed his occupation for another outside the plastics industry. Two years later, in 1937, he resumed work with plastics, now heating blocks of the plastic compound prepared in the earlier process and feeding the softened material into presses. In both processes the workers were affected by pitch warts, but in the first the fume was much heavier, and in addition to the warts some men, including the patient, also developed a mottled telangiectatic erythema of the forearms and neck. In 1949 he noticed a small nodule on the back of his neck, increasing in size for about nine months before biopsy showed a squamous-celled carcinoma. Treatment with radium needles was effective. At about the same time an ulcer developed on the left forearm, also shown by biopsy to be an epidermoid carcinoma of the skin. This ulcer healed after treatment with radium needles and neither lesion recurred subsequently.

For the last fifteen years he had complained of a cough productive of white sputum; six months before admission his first hæmoptysis occurred and was repeated at intervals of one or two weeks. His general health remained good. Examination revealed well-healed scars of treated epitheliomata on the dorsum of the left forearm and on the posterior aspect of the neck. The dorsum of the forearms and hands showed a patchy telangiectatic erythema; there were three small keratinised pitch warts on the left hand. His voice had been husky for many years. There were no abnormal physical signs in the respiratory system. A chest X-ray showed a circumscribed opacity at the left hilum. There was neither clinical or radiological evidence of asbestosis.

No abnormality was found on laryngoscopy. Bronchoscopy showed a normal right bronchial tree. A small quantity of pus was present in the left bronchus, and on the posterior wall of the branch to the left lower lobe, at the site of the apical orifice, there was a small sessile tumour (6 by 6 mm.). Biopsy confirmed a squamous carcinoma, although three specimens of fresh sputum had contained no neoplastic cells. On August 5, 1952, Mr. Vernon Thompson performed a left lower lobectomy, noting at operation plaques of hyaline fibrosis upon the parietal pleura. The patient made an uneventful recovery, and has remained free of symptoms for six months subsequently.

Pathological Specimen.—Dr. D. J. O'Brien.

Macroscopic.—Anthracotic hilar lymph nodes up to 2·3 by 0·8 cm. without obvious growth. Granular, grey, friable tumour projecting into main bronchus at cut surface of removal and extending along the subapical bronchus for a

distance of 2·2 cm. The bronchus distal to this is dilated and lined by a thick, rigid granular mucosa. 3·5 cm. from beyond the margin of this mass there is a soft granular grey tumour tissue extending from the bronchus into the parenchyma for 3·8 cm. and approaching to within 0·7 cm. of the pleura of the lateral surface of the lung. Dilatation of apical bronchi up to 1·2 cm. diameter and small flecks of golden-yellow material in posterior angle. The parenchyma of basal bronchi is normal.

Microscopic.—Squamous and horny carcinoma of main bronchus of left lower lobe, extending along subapical bronchus and infiltrating the parenchyma close to the pleura. Reactive hyperplasia in five hilar lymph nodes.

Discussion

There is an obvious hazard to the lungs in occupations such as pitch-handling, the production of corkstone and artificial fuel, certain processes in the plastics industry, road tarring and chimney sweeping, and others which involve the inhalation of known carcinogens. In spite of this there have been few clinical reports and fewer statistical enquiries. Fischer-Wasels (1936) denied that tar or pitch had ever produced a pulmonary carcinoma in man, although admitting the relationship in animals. From a statistical survey Kennaway and Kennaway (1936) concluded that road tar had no effect on the general population, and that " such data as are available suggest that coal-tar in the atmosphere, whether derived from the roads, domestic chimneys, or any other source, does not readily give rise to cancer of the lung." They found, however, that the morbidity ratio of carcinoma of the lung for gas stokers and coke-oven chargers was 342, compared with 100 for the general population, but they emphasised the high sampling error owing to the small numbers of cases. In a later survey (1947) of the occupation of 38,418 fatal cases of carcinoma of the bronchus, they calculated that workers with coal gas and tar suffered an increased incidence 2·5 times as great as normal, although again the error was high in numerically small trades. More recently Doll (1952) has shown that in gas workers the incidence of pulmonary carcinoma was twice the normal (25 deaths as against 13·8 expected), the high mortality chiefly affecting workers producing gas and treating its waste products. Examining other causes of death amongst gas workers, he found no corresponding difference from the expected numbers.

Kuroda (1937) gave a brief account of twelve cases of lung carcinoma in the Yawata steel workers. He did not state among how many men these cases arose, but all were gas workers, intermittently exposed to yellow-brown tarry fume emitted from gas generators at a high temperature. Kawahata (1938) reported, apparently from the same source, 21 cases occurring within six years, all of whom were gas generator workers frequently exposed to a hot tar-containing fume. The development of carcinoma of the lung occurred after an average interval of sixteen years; the absence of skin tumours was attributed to frequent washing habitual in Japanese workmen. Kuroda and Kawahata (1936) found that among 18,000 workers, 61 cases of pulmonary carcinoma were diagnosed within five years. They found the morbidity for the general population of the steel works to be 1 per cent., whereas for gas generator workers it was 6·69 per cent. and for engine drivers 3·36 per cent.

The upper lobes of the lungs were predominantly affected. The gas concerned was found to contain 0·7 per cent. of tar of which 62·67 per cent. was pitch.

Since Rösch (1923) reported the case of a paraffin worker in whom carcinomata of the skin, stomach and lung occurred simultaneously, a number of similar cases have occurred in tar workers. Koelsch (1934) gave an isolated instance of a locksmith, exposed to tar in a factory for twenty-four years, who developed a lung tumour.

In Matras's (1935) case a 66-year-old man had been employed for fifty-two years in a tar factory, burning soot for forty-four years. His skin was diffusely pigmented and biopsy showed malignant changes. Consolidation in the right perihilar region was strongly suggestive of a tumour, though histological confirmation was not obtained.

Müllschitzky (1939) gave an account of a 66-year-old tar distiller who underwent operations for genital carcinoma fourteen and eleven years before his final admission. Many keratoses were present on the skin. Two years earlier his right pinna had been excised for a carcinoma, and for one year he had suffered from dyspnœa on exertion, chest pain and loss of weight. Necropsy showed a squamous-celled carcinoma of the upper lobe of the right lung with extensive metastases.

Experimental evidence for the production of pulmonary carcinomata by pitch and similar substances is strong, but its relevance to man remains doubtful (Goldblatt, 1950). Murphy and Sturm (1925) found that spaced applications of tar to the skin of mice, three times weekly for four months, might produce lung carcinoma without change in the skin. Intratracheal insufflation of tar and other substances has been repeatedly found to cause pulmonary tumours in mice (Schabad, 1932; Shimkin, 1939; Campbell, 1934, 1937, 1939), and subcutaneous injection of carcinogenic hydrocarbons is similarly effective (Andervont, 1937a, 1937b). Bonne and Stoel (1926) showed that a high incidence of pulmonary tumours occurred in untarred mice sharing a cage with tarred animals. The numbers were small, but suggested that absorption had occurred by licking their painted cage mates. In human cases, granted reasonable cleanliness, there seems no reason to postulate that the skin is an important route of absorption.

Bloch and Dreifuss (1921) showed that the higher boiling fractions of tar (over 300° C.) produced the highest proportion of skin carcinomata experimentally. After four months 100 per cent. of animals were affected. Working with tobacco tars, Flory (1941) obtained similar results with fractions distilling at 350°-700° C., but Kling, Samssonow and Heros (1938a and b) found that volatile fractions also contained effective carcinogens.

Both on experimental and clinical grounds some authors have suggested the importance of heat in carcinogenesis (Hueper, 1952), but this is not yet established. Findlay (1925) found a single application of hot tar (70° C.) effective in producing skin carcinoma in mice. Kuroda and Kawahata (1936 and 1938) thought that heat was an additional factor in their gas workers. These authors also stressed the long latent period (an average of sixteen years) before the development of pulmonary tumours, and Hueper (1951) gives a range of from five to forty years.

Conclusions

The evidence available indicates that pitch and related substances are effective causes of pulmonary carcinoma in animals. In man there have been few cases reported, and the evidence is inconclusive, which is surprising in the face of so obvious a hazard. When Kennaway and Kennaway (1936) surveyed fatal pulmonary carcinoma no case was related to foregoing asbestosis. Yet asbestosis now stands in well-recognised relationship to carcinoma (Wyers, 1947). It seems probable that at the present time the relationship of pitch to pulmonary carcinoma is analogous, and that the possibility is generally overlooked, even in men under constant and heavy exposure. This can only be if such a complication of pitch exposure is not sufficiently frequent to be immediately obvious. The difficulties are further increased by a long latent period in the development of carcinoma, and by the few individuals who are exposed to high concentrations of pitch.

Hueper (1950) has already indicated that the question merits serious attention. The evidence stated suggests that a large-scale survey of causes of death among the relevant occupations (similar to that undertaken by Doll) is timely and worth while. Meantime it seems advisable for pitch and tar workers to have, as Matras recommends, regular chest investigations carried out.

Summary

The case reported concerns a pitch worker who developed a squamous-celled carcinoma of the lung, having previously had multiple skin carcinomata.

The literature regarding carcinogenesis due to pitch and related compounds is reviewed, with particular regard to the lung. There have been few cases of pulmonary carcinoma reported among pitch workers. A survey of workers in such occupations might reveal significant numbers of cases, not otherwise evident. Meanwhile periodic chest X-rays are advisable for workers in these industries.

I wish to thank Dr. Kenneth Perry for his suggestion of reporting this case, and for his helpful criticism; to Dr. W. Shanks for information regarding the cutaneous lesions; and to Dr. D. J. O'Brien for the pathological report.

REFERENCES

ANDERVONT, H. B. (*a*) (1937): Cancer Problem Symposium. American Assoc. for Advancement of Science, 62-66.
(*b*) (1937): *Pub. Health Rep.*, **52**, 1584.
BERENBLUM, I., and SCHOENTAL, R. (1947): *Brit. J. Cancer*, **1**, 157.
BLOCH, B., and DREIFUSS, W. (1921): *Schweiz. med. Wschr.*, **2**, 1033.
BONNE, C., and STOEL, G. (1926): *C. R. Soc. de Biol.*, **94**, 649.
BUNBURY, H. M. (1950): Chambers's Encyclopædia, New Edn., Vol. 13, p. 462, George Newnes, London.
CAMPBELL, J. A. (*a*) (1934): *Brit. J. Exper. Path.*, **15**, 287.
(*b*) (1937): *Brit. J. Exper. Path.*, **18**, 215.
(*c*) (1939): *Brit. J. Exper. Path.*, **20**, 122.
COHEN, J. B., and RUSTON, A. G. (1925): " Smoke: A Study of Town Air," 2nd edn., p. 5. Edward Arnold, London.
DAVIDSON, M. (1948): " A Practical Manual of Diseases of the Chest, 3rd edn., p. 548. Oxford University Press, London.

DAVIDSON, M., SMITHERS, D. W., and TUBBS, O. S. (1951): "The Diagnosis and Treatment of Intrathoracic New Growths," 1st edn., p. 87. Oxford University Press, London.
DOLL, R. (1952): *Brit. J. Indust. Med.*, **9**, 180.
DOLL, R., and BRADFORD HILL, A. (1952): *Brit. Med. J.*, **2**, 1271.
FINDLAY, G. M. (1925): *Lancet*, **1**, 714.
FISCHER-WASELS, B. (1936): *Frankfurt. Ztschr. f. Path.*, **49**, 145.
FLORY, C. M. (1941): *Cancer Research*, **1**, 262.
GOLDBLATT, M. W. (1950): *Practitioner*, **164**, 404.
GRAHAM, E. A. (1951): *Bull. N.Y. Acad. Med.*, **27**, 261.
HADDOW, A., and KON, G. A. R. (1947): *Brit. Med. Bulletin*, **4**, 314.
HELLER, J. R. (1950): *Amer. Med. Ass. Arch. Indust. Hyg. and Occup. Med.*, **20**, 390.
HUEPER, W. C. (1950): *South Med. Jour.*, **43**, 118.
HUEPER, W. C. (1952): *Amer. Med. Ass. Arch. Indust. Hyg. and Occup. Med.*, **5**, 204.
KATZ, K. (1927): *Ztschr. f. Krebsforsch.*, **25**, 368.
KAWAHATA, K. (1938): *Gann.*, **32**, 367.
KENNAWAY, N. M., and KENNAWAY, E. L. (1936): *J. Hyg.* (Camb.), **36**, 236; (1947) *Brit. J. Cancer*, **1**, 260.
KIKUTH, W. (1925): *Virch. Arch. f. path. Anat.*, **255**, 107.
KLING, A., SAMSSONOW, N., and HEROS, M. (*a*) (1938): *Bull. Acad. de med.*, Paris, **119**, 439. (*b*) (1938): *Compt. rend. Acad. de sc.*, **206**, 1268.
KOELSCH, F. (1934): *Arch. f. Gewerbepath.*, **5**, 454.
KURODA, S. (1937): *Indust. Med.*, **6**, 304.
KURODA, S., and KAWAHATA, K. (1936): *Ztschr. f. Krebsforsch*, **45**, 36; (1938) *Jap. Jour. Med. Sci., VIII*, Int. Med., Pediat. and Psychiat., 5, 41 (Proceedings of annual meeting).
MCCRAE, T., FUNK, E. H., and JACKSON, C. (1927): *J. Amer. Med. Ass.*, **89**, 1140.
MATRAS, — (1935): *Zentralbl. f. Haut- u. Geschlrchtskr.*, **50**, 648.
MÜLLSCHITZKY, A. (1939): *Dermat. Wchnschr.*, **109**, 973.
MURPHY, J. B., and STURM, E. (1925): *J. Exper. Med.*, **42**, 693.
NORRIS, G. W., and LANDIS, H. R. M. (1938): "Diseases of the Chest," 6th edn., p. 665. W. B. Saunders, Philadelphia.
O'DONOVAN, W. J. (1920): *Brit. J. Dermatol.*, **32**, 215 and 245.
PASSEY, R. D. (1922): *Brit. Med. J.*, **2**, 1112.
PERRY, K. M. A. (1952): in "Diseases of the Chest," 1st edn., p. 261. Butterworth, London.
POTT, P. (1775): "Chirurgical Observations." London. (Cit. Haddow and Kon.)
RUBIN, E. H. (1947): "Diseases of the Chest," 1st edn., p. 462. W. B. Saunders, Philadelphia.
SCHABAD, L. (1932): *Ztschr. f. Krebsforsch.*, **38**, 154.
SHIMKIN, M. B. (1939): *Amer. J. Cancer*, **35**, 538.
VOLKMANN, R. (1875): "Beiträge zur Chirurgie," Leipzig, pp. 370-81.
WYERS, H. (1949): *Postgrad. Med. J.*, **25**, 631.
YAMAGIWA, K., and ICHIKAWA, K. (1916): *Mitt. med. Fak. Tokyo*, **15**, 295.
YOUNG, M., and RUSSELL, W. T. (1925): M.R.C. Special Report Series, No. 99. An Investigation into the Statistics of Cancer in Different Trades and Professions.

VITAMIN B_{12} AND PULMONARY TUBERCULOSIS

By Kenneth Marsh

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One of the minor difficulties in the treatment of a patient with pulmonary tuberculosis, especially during a long stay in a sanatorium, is that of sustaining his interest in food. Coupled with this is the usual aim of increasing his weight and improving the sense of well-being. Various expedients, such as aperitifs containing bitters, or injections of insulin half an hour before a meal, to lower the blood sugar and produce a sensation of hunger have only a transient effect.

If the patient has recently undergone a major operation he will be in " nitrogen debt " and the need to increase his caloric and his protein intake as rapidly as possible is all the more apparent. Unfortunately, many patients after a major operation have very little or no appetite, and the capricious appetite that they may subsequently develop usually craves for carbohydrates rather than protein, even in its most appetising form.

Studies on the optimum calorie and protein intake of patients with pulmonary tuberculosis have been made by Payne (1951), who recommended a basic daily diet of 2,800-3,000 calories containing 90 grammes of protein. Supplements of vitamin B, crude liver extract and ascorbic acid should be given, together with methionine (5 g.) or choline (5 g.). Such a diet is not always easy to supply or maintain, and Payne used in addition a protein digest of 1·5 g. protein per kilo, but the appetite frequently fails at the prospect of such large regular meals. A study of recent literature suggested that vitamin B_{12} might be useful in indirectly stimulating the appetite and, coupled with protein supplementation, might help in the processes of repair and healing, especially as there is some evidence that vitamin B_{12} and methionine are intimately linked in metabolism (Schaefer *et al.*, 1950).

When the work of Wetzel *et al.* (1949) and Chow (1951) were first reported it was thought that vitamin B_{12} might have some specific effect in improving chronically underweight and ill children. Wetzel and his colleagues gave 10 μg. of vitamin B_{12} daily to eleven children who were undersized because of long illness or simple malnutrition. The preparation was given by mouth and they concluded that there was considerable improvement in the height, weight and general nutrition of these children. In further work Wetzel *et al.* (1952) claimed to substantiate this conclusion.

Salmi (1950) found that in infants with hypoproteinæmia vitamin B12 caused a renewal of growth with " normalisation of proteinæmia, amino-acidæmia, iron blood level and cholesterinæmia." Downing (1950), however, did not find any appreciable difference between premature infants receiving vitamin B12 and controls not receiving it, in respect of average total weight gain, average daily gain and average time to reach a weight of 2·5 kg. Glaser

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et al. (1950) gave vitamin B_{12} to the smaller of seven sets of twins, and in only one instance did the treated infant surpass his control twin in weight gain. Mitchell *et al.* (1951) found no improvement over controls when vitamin B12 and folic acid were given to premature infants. Jamieson (1952) gave vitamin B_{12} by mouth to children convalescent from tuberculous meningitis, and he maintained that there was a significant gain in weight. His figures do not, however, confirm this (Zerny, 1952). Furthermore, Benjamin and Pirrie (1952), who gave vitamin B_{12} orally to children who had a chronic disabling disease such as bronchiectasis or asthma, or who were recovering from an acute illness, were unable to show any improvement in weight gain.

It should be noted that in all these cases the vitamin was given by mouth.

Gershon-Cohen (1951) gave a liver " cocktail " daily for three months to thirty-one patients with pulmonary tuberculosis. A further series of twenty-nine patients were used as controls. He maintained that the individual weight gain in the group receiving the " cocktail " was almost twice that in the control, and in a further small series it was noted that patients receiving streptomycin alone had a slight weight loss. He made no suggestion about the agent, although at that time it was thought that vitamin B_{12} might be a possible factor. However, in view of the work of Yudkin (1952), who gave a powdered liver preparation to healthy children and found that they gained more weight than controls, the possibility of some factor analogous to the " G " factor of Yudkin must be considered.

Recent work on the animal protein factor (A.P.F.) suggests that it may be similar to vitamin B_{12} and that this factor may be responsible for the increase in the growth rate of animals and chickens. Furthermore, Black and Bratzler (1952) showed that albino rats on a basal diet given streptomycin and vitamin B_{12} gained more weight in a shorter time than control animals. They thought that the benefit from the combination of vitamin B_{12} and antibiotics is probably effected through the influence of such supplements on overall energy metabolism.

Investigation

(*a*) *Vitamin B_{12}*

It was thought to be worth while to investigate the effect, especially on the appetite, of giving 50 μg. of vitamin B_{12} intramuscularly three times a week to sanatorium patients suffering from pulmonary tuberculosis who were underweight—that is, under their weight on admission, which itself was below their average weight when previously healthy. The vitamin was given for at least three months and longer in some cases. In addition the vitamin was given to patients who had undergone a thoracoplasty or lobar resection for their pulmonary tuberculosis.

An analysis of several days' diets showed that the diet contained 2,890 calories and 72 g. of protein. The diet was supplemented daily in this investigation with 30 grains ferrous sulphate, vitamin A (6,000 I.U.) and vitamin D (1,000 I.U.) in capsule form, and 200 mg. of ascorbic acid.

Pairing of patients by age, sex and type of disease as well as by treatment meant that few numbers were available for study over a period of three months.

Patients were weighed weekly. The hæmoglobin, total red cell count and sedimentation rate (Westergren) were measured monthly. These four measurements were easy to make, and the degree of error was reduced as far as possible by ensuring that the patient was weighed in the same clothes each time. The blood investigations were all performed by the same person and were done in the morning within one hour of breakfast. Weekly estimations were made, but only the results after three months' treatment were used. Several patients, especially the surgical ones, had these procedures done more frequently and white cell counts were also done, but not as a part of the investigation. Altogether, nine patients, seven males and two females and their controls were studied. Of the five men who had medical treatment, three had postural retention, one with additional chemotherapy, and one had chemotherapy alone. The fifth patient had a phrenic nerve crush and pneumoperitoneum. One patient had a seven-rib thoracoplasty and the other had a draining empyema; neither had chemotherapy during the course of this trial. One woman had a thoracoplasty; the other had a lobectomy followed by a thoracoplasty and she received chemotherapy. Routine chemotherapy consisted of streptomycin 2 g. twice a week and 12 g. P.A.S. daily for at least three months. Vitamin B12 was given in the surgical cases as soon as the surgery was completed, and in the medical cases when treatment was begun.

(*b*) *Vitamin B_{12} and peptone*

Four patients, three men and one woman, and four controls, took a peptone preparation *ad libitum*, but none was able to maintain a regular daily intake because of its unpalatable nature.

(*c*) *Vitamin B_{12} and liver preparation*

On the assumption that the "liver cocktail" of Gershon-Cohen might contain some unknown factor a somewhat similar commercial preparation was used. This also contains additional peptone and vitamin B_{12}. It proved to be somewhat more palatable than peptone alone, but patients could not take specific amounts daily for any length of time, and it was necessary to give the preparation *ad libitum*. However, fourteen men and twenty-four women persevered for three months. Eight men had undergone operations and six had purely medical treatment. Five women had operations and nineteen received only medical treatment.

Results

In reply to questioning none of the patients complained of the injections, nor were there any untoward reactions. None felt any better or worse, or noted any change in their appetite or sense of well-being. There was no statistically significant difference in the gain in weight, fall in B.S.R., increase in hæmoglobin percentage or alteration in total red cell count in the two groups. Similarly vitamin B_{12} and powdered liver preparation made no difference in another series of patients.

Conclusions

Vitamin B_{12} was given to nine patients suffering from pulmonary tuberculosis. No improvement in the gain in weight, in hæmoglobin concentration, red cell count or sedimentation rate over controls was noted. Peptone supplement which was very unpalatable was given to four patients, and a commercial preparation containing peptone and vitamin B_{12} was given to another thirty-eight patients. Again no improvement was noted.

I am indebted to Dr. T. W. Lloyd, St. Wulstan's Hospital, Malvern, for permission to publish some results obtained in that hospital, to Evans Medical Supplies Ltd. for supplies of vitamin B_{12} and liver preparation, and Armour Laboratories for a supply of peptone supplement.

REFERENCES

Benjamin, B., and Pirrie, G. D. (1952): *Lancet*, **1**, 264.
Black, A., and Bratzler, J. W. (1952): *J. Nutrit.*, **47**, 159.
Chow, B. F. (1951): *Ibid.*, **43**, 323.
Downing, D. F. (1950): *Science*, **112**, 181.
Gershon-Cohen, J. (1951): *Amer. J. digest. Dis.*, **18**, 215.
Glaser, K., Parmelee, A. H., and Plattner, E. B. (1950): *Pediatrics*, **5**, 130.
Jamieson, S. R. (1952): *Brit. med. J.*, **1**, 83.
Mitchell, T., Etteldorf, J. N., Tuttle, A. H., and Clayton, G. W. (1951): *Pediatrics*, **8**, 821.
Payne, H. M. (1951): *Pub. Hlth. Rep.*, **66**, 1263.
Salmi, L. (1950): *Clin. pediat.*, **32**, 617.
Schaefer, A. E., Salmon, W. D., Strengt[illegible] D. R., and Copeland, D. H. (1950): *J. Nutrit.*, **40**, 95.
Wetzel, N. C., Fargo, W. C., Smith, I. H., and Helikson, J. (1949): *Science*, **110**, 651.
Wetzel, N. C., Hopwood, H. H., Kuechle, M. E., and Grueninger, R. M. (1952): *J. clin. Nutrit.*, **1**, 17.
Yudkin, J. (1952): *Brit. med. J.*, **1**, 1388.
Zerny, C. J. (1952): *Ibid.*, **1**, 329.

MEDIASTINAL NEUROFIBROMATOSIS

WITH REPORT OF A CASE SHOWING MULTICENTRIC MALIGNANT METAPLASIA

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The skin manifestations (multiple, sessile and pedunculated tumours) of the clinical syndrome known as neurofibromatosis were first described by R. W. Smith in 1849. They were again described independently by von Recklinghausen in 1882, by whose name the disease is now generally known. Since then many authors have described manifestations of this disease other than the cutaneous neurofibromata, such as pigmentary changes in the skin and neurofibromatous involvement of the central nervous system, internal organs and skeletal system. The majority of cases reported in the literature are of a complicated or unusual nature, and, though cases of malignancy have been recorded from time to time, an assessment of the statistical incidence of malignancy in this disease is impossible.

The very variable incidence of malignancy in the series of cases reported by various observers is shown in the following table:

TABLE I

Table showing Percentage of Malignancy in Cases of Primary Neurogenic Tumours reported by Various Authors

Author	*Cases of primary neurogenic tumour*	*Percentage of malignancy*
Courvoisier, 1886	800	6·6
Garre, 1892	—	12
Hosoi, 1931	500	13
Kent *et alia*, 1944	78	14·3
Kent *et alia*, 1944	18	41
Blades, 1946	30	3·3
Curreri *et alia*, 1949	7	13·3
Brewer *et alia*, 1949	17	58·8
Harrington, 1949	51	5·9
Arbuckle, 1949	11	18·1
Godwin *et alia*, 1950	—	13
Victa and Pack, 1950	—	Less than 13
Barberg, 1951	76	1·05
Preston *et alia*, 1952	61	16

Distribution of Lesions

The commonest lesions are cutaneous, occurring on the trunk, face and extremities along the course of nerve trunks. These are generally accompanied by pigmentary changes which may take the form of " tâches de couleur, café au lait," deep " brunâtre " and large areas of pigmentation.

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Intra-thoracic Neurogenic Tumours

Harrington (1949) described 51 primary nerve tumours of the posterior mediastinum with an incidence of 5·9 per cent. malignancy. Godwin and his co-workers (1950) state that " the diagnosis of neurogenic tumour is relatively certain by radiographic examination when a spherical or lobulated shadow is seen in the paravertebral gutter." Support of such a diagnosis is often afforded by the skin stigmata of von Recklinghausen's disease.

Kent and his co-workers (1944) collected 78 cases of primary intrathoracic neurogenic tumours reported in the literature with an incidence of 15·3 per cent. of malignancy. They added 18 new cases with an incidence of 41 per cent. malignancy. Godwin and his colleagues (1950) emphasised the importance of distinguishing between diffuse and encapsulated neurilemoma because about 13 per cent. of the diffuse type become malignant.

The cutaneous lesions constitute the classical forms of diffuse neurilemoma. The encapsulated neurilemoma is typified by the acoustic nerve tumour, and though this type rarely becomes malignant a case has been reported by Saxen (1948).

The origin of the encapsulated neurilemoma in Schwann cells was experimentally demonstrated by Nageotte (1932) and Masson and Simar (1930), and Masson (1932) concluded that encapsulated neurilemoma in man were constituted almost exclusively of Schwann cells, from a comparative histological study of such tumours and those experimentally produced.

Del Rio Hortega (1943) demonstrated that the origin of the diffuse neurilemoma lies in certain specific cellular elements which he designates as lemmocytes. These elements had not been previously recognised owing to the inadequacy of routine histological staining technique, but became discernible when a modified silver carbonate technique was employed.

We report a case of multiple neurofibromatosis with a large intrathoracic mass complicated by sarcomatous changes.

Case Report

J.C.A., male, age 44, was referred to one of us (P.E.) on 28.5.53, complaining of a cough of several years' duration associated with a trace of mucoid sputum which had never been blood-stained.

The *history of his present condition* shows that he had been complaining of lassitude and anorexia for eighteen months, but there had been no appreciable loss of weight.

He had become increasingly breathless on exertion for some three months, and during the last two weeks he was very breathless even at rest.

He had lost no appreciable weight and complained of lassitude and general malaise, sweating and pain at the right base, aggravated by deep breathing.

His *previous history* revealed what had been regarded as generalised neurofibromatosis since early childhood. Apart from this there had been nothing significant nor was there anything noteworthy in the *family history*.

On *clinical examination* he was afebrile, markedly breathless and cyanosed. His pupils were equal, reacting to light and accommodation. Retinoscopy showed no abnormality. There was no evidence of finger clubbing, but he had gross enlargement of the right thumb. He had marked cutaneous pigmentary

changes (café-au-lait spots) with widespread, mainly pedunculated, tumours (Fig. 1) on the face, trunk and extremities. There was no evidence of disease in the upper air passages. There were no glands in the neck.

Clinical examination of the chest showed some kyphoscoliosis. The apex beat was 5 inches from the middle line. The rhythm was regular. The rate was normal. The heart sounds were normal. The blood pressure was 150/100. The right hemithorax showed restricted movements. There was absolute dullness to percussion over the whole of the right hemithorax and the breath sounds were virtually absent. The physical signs were those of a right-sided hydrothorax.

X-ray examination of the chest showed an opaque hemithorax with the heart displaced to the left. After repeated aspirations serial skiagrams and tomograms showed that the lung was compressed and surrounded by peripheral tumour growth (Figs. 2 and 3).

Following paracentesis of the pleura 500 c.c. of hæmorrhagic fluid was aspirated and further aspirations showed persistence of the hæmorrhagic fluid.

Repeated examination of the sputum showed no carcinoma cells and no organisms.

Bronchoscopy showed the cords, trachea and carina normal. A good view of all orifices was obtained on the right side. There was an excessive amount of frothy mucoid material in the whole of the right bronchial tree; otherwise no abnormality was detected. The left bronchial tree was normal.

Clinical examination of the abdomen showed enlargement of the liver (three fingers' breadth below the subcostal margin). The spleen and kidneys were not felt.

There was nothing noteworthy in the *central nervous system.*

His condition gradually deteriorated and finally he developed high pyrexia, proptosis of the right eye and a mass over the left buttock which increased considerably in size in seven days, and he finally succumbed two months after admission.

Report on Post-mortem Examination (L.W.P.)

External Appearance.—The body showed generalised molluscum fibrosum. Multiple nodules ranging from 2 mm. up to the largest diameter of 6 cm. in the right groin. These were mostly pedunculated. There was a massive tumour in the left gluteal region. This on incision proved to be of a rubbery consistency showing necrotic degeneration in a neurofibroma of the sciatic nerve. The macroscopic appearance indicated malignant change. The right thumb was grossly enlarged, as shown in the photograph, owing to diffuse neurofibromatosis (Fig. 1).

Skeletal System.—Dissection of the chest wall showed multiple millet-like nodules in the rectus abdominus. There were also multiple larger nodules in the intercostal muscles. The left gluteal muscle showed a large nodule. The right mammary gland was enlarged and showed gynæcomastia.

Thorax.—The sternum on the right side was densely adherent to the thoracic contents. These consisted of a massive tumour of white appearance and rubber-like consistency which had manifestly arisen multicentrically from the peripheral part of the chest. A special dissection was carried out to show the distribution of the tumour nodules. A photograph of the bony thoracic cavity shows the peripheral tumour lining the perietal pleura and extending on to the diaphragm. This caused compression and collapse of the right lung and

it was apparent that peripheral invasion of the lung by tumour tissue had occurred (Fig. 4).

A special photograph depicting the posterior aspect of the eviscerated thoracic contents shows that the trachea and bronchi are free from neoplasm. Thus, the tumour has not arisen primarily in the respiratory tract, but has invaded the lung from without. A photograph of the anterior part of the right side of the chest shows nodules projecting into the pleura and also into the diaphragm. The compressed lung is also shown.

The median section of the sternum depicts part of the tumour impinging upon the inner aspect of the sternum.

The growth caused displacement of the heart to the left.

The distal part of the tumour, extending over the diaphragm, attained a depth of 10 cm.

Abdomen.—The abdominal lymph glands showed infiltration. The liver was enlarged and showed nutmeg congestion. The spleen was enlarged and showed cardiac congestion. The suprarenals were normal. The pancreas was congested but otherwise normal. The stomach showed congestion and terminal minute toxic acute ulcers with some gastrostaxis.

Central Nervous System.—The brain appeared normal. It was removed *in toto* and placed in fixative solution for further dissection after fixation.

Cause of Death.—Sarcomatous degeneration in molluscum fibrosum; pulmonary collapse; cardiac failure.

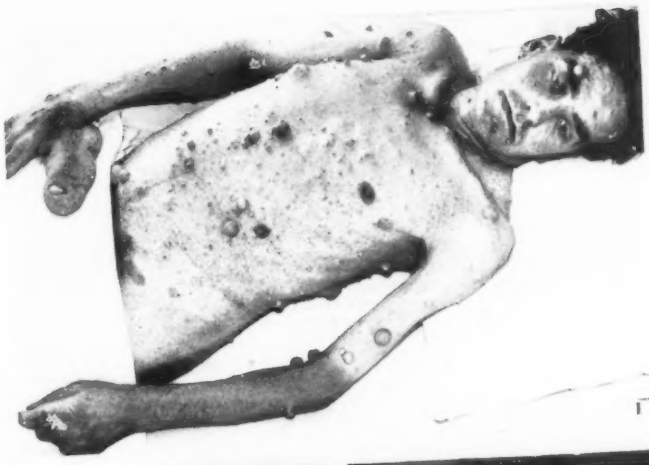
Discussion

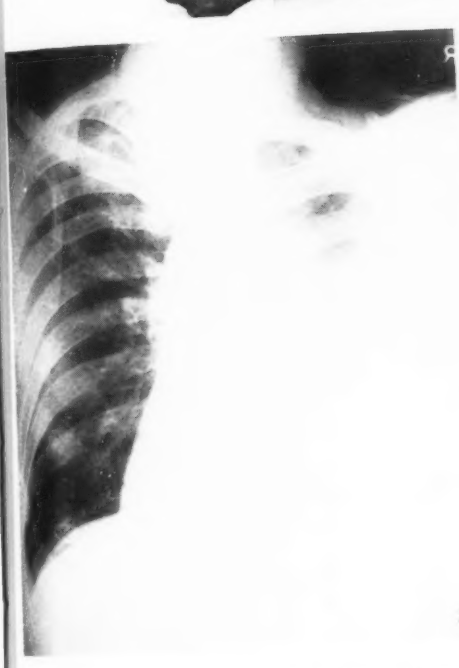
A case of mediastinal tumour with hæmorrhagic effusion into the pleura and malignant metaplasia has been presented. It is clear from the radiogram (Fig. 2) and tomogram (Fig. 3) and also from the post-mortem preparations that this tumour did not arise directly in the trachea, bronchi or peripheral part of the lung (Fig. 5). The lung was compressed, and to some extent invaded by tumour tissue arising in the chest wall, the origin being manifestly multicentric. The combination of clinical and radiological findings together with the negative bronchoscopy and absence of neoplastic cells from both the sputum and pleural effusion left little doubt about the diagnosis. It is of interest to see how the chest radiological findings, including the tomogram, compare, from the point of view of tumour growth, with the macroscopic specimen of the lung. In other words, the tomogram represents an autopsy of the living subject.

Generalised neurofibromatosis had been present in this patient from an early age. The incidence of this syndrome, according to Preiser and Davenport (1918), is about once in every 2,000 patients that present themselves to medical clinics or to private practitioners. The incidence in the chest, however, is less clearly defined. According to Curreri and Gale (1949), 92 per cent. of posterior mediastinal tumours are neurogenic.

The incidence of malignancy in generalised neurofibromatosis has been very variably reported by different workers, as shown in the table. There is a similar difference of opinion in regard to the incidence of malignancy of neurogenic tumours of the chest (Godwin *et al.*, 1950; Kent *et al.*, 1944).

It is our opinion that the various and conflicting accounts of the incidence of malignancy in generalised neurofibromatosis, and particularly neurofibromatosis of the chest, are due to a certain confusion in the minds of clinical workers





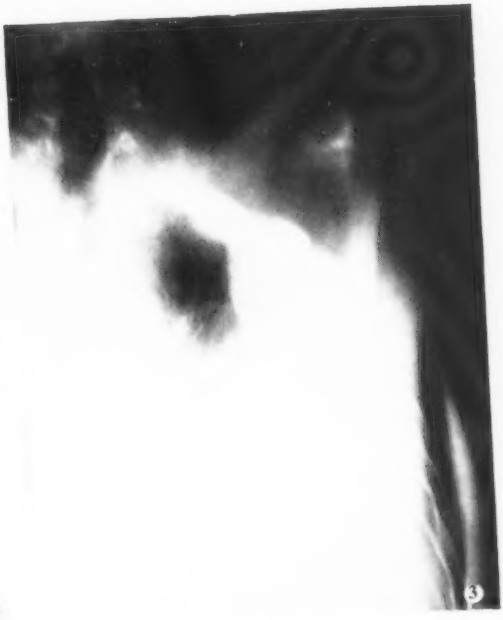
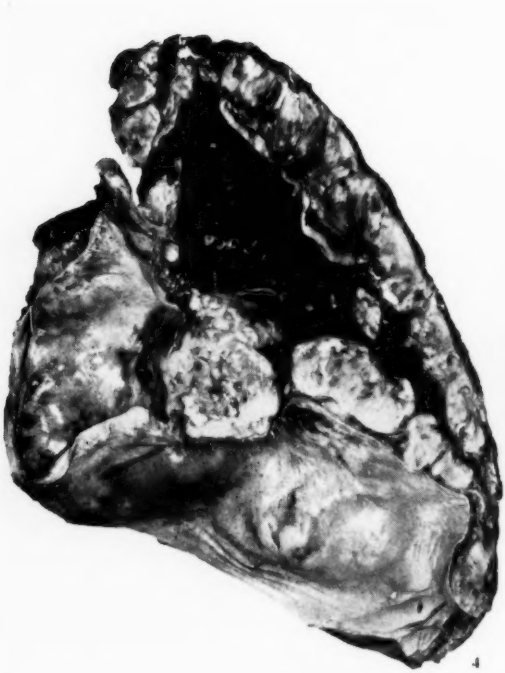


Fig. 1.—Clinical photograph from the case of neurofibromatosis showing the skin lesions.

Fig. 2.—X-ray of the chest showing opaque right hemithorax (taken from posterior aspect).

Fig. 3.—Tomogram (cf. Fig. 2) showing the nodular character of the growth (taken from posterior aspect).



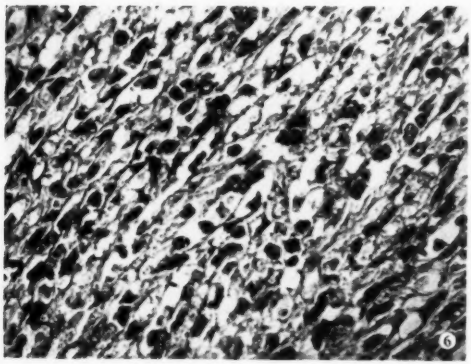


FIG. 4.—Macrophotograph of right side of thorax (anterior part) seen from behind.

FIG. 5.—Macrophotograph showing trachea, bronchi and lungs seen from posterior aspect. The nodular growth compressing the right lung is well shown.

FIG. 6.—Photomicrograph showing a characteristic malignant field. (H and E) (8 mm. apo.).

as to the precise nature of the pathological entity with which they are dealing.

TABLE II

TABLE SHOWING SYNONYMOUS TERMS FOR NEUROGENIC TUMOURS

Encapsulated neurilemoma	*Diffuse neurilemoma*
Schwannoma	Neurofibroma
Specific nerve sheath tumour	Myxoid neurinoma
Neurinoma	Neurilemoblastoma
Perineural fibroblastoma	von Recklinghausen's disease
Peripheral glioma	Lemmocytoma
Schwannoglioma	Molluscum fibrosum
Palisaded neurinoma	
Acoustic neurinoma	

Table II, showing synonymous terms, indicates that there are two main types of neurogenic tumour which may occur in the chest. The one is encapsulated, generally non-malignant and typified by the acoustic nerve tumour; the other is diffuse, often malignant, and typified by von Recklinghausen's disease. Both of these types must be differentiated from pleural mesotheliomas (Benoit and Ackerman, 1953). The neuropathology of the two main types of neurogenic tumour has been worked out by del Rio Hortega (1943) and confirmed by Scharenberg (1952) and by John and Ormea (1951).

Although both the Schwann cell and the lemmocyte originate from displaced elements of the neural crest, they are fundamentally different types of cell and give rise to different types of peripheral glioma. The present case is histologically of the diffuse type (Fig. 6) and lemmocytes can be demonstrable in special sections. Malignancy has been of multicentric origin, as indicated by the nodularity and widespread distribution of the chest nodules and the fortuitous development of concomitant malignancy in the sciatic nerve.

Summary

A case of malignant mediastinal neurofibromatosis, with multicentric malignant metoplasia, which came to autopsy is presented. The variable incidence of malignancy in generalised neurofibromatosis is discussed.

REFERENCES

ARBUCKLE, R. K. (1949): *Amer. J. Roentgenol.*, **62,** 52.
BARBERG, A. (1951): *Act. psychiat. et neurol. supp.*, 71.
BENOIT, H. W., and ACKERMAN, N. K. (1953): *J. Thorac. Surg.*, **25,** 4.
BLADES, B. (1946): *Ann. Surg.*, **123,** 749.
BREWER, L. A., and DOLLEY, F. S. (1949): *Amer. Rev. Tuberc.*, **60,** 419.
COURVOISIER, L. G. (1886): Basel: Benno Schwabe.
CURRERI, A. R., and GALE, I. W. (1949): *Arch. Surg.*, **58,** 797.
DEL RIO HORTEGA (1943): *Archivios de histologia, Normal y Pathologica*, **1,** 373.
GARRE, C. (1892): *Beitr. Z. Klin. Chir.*, **9,** 465.
GODWIN, J. T., WATSON, W. L., POOL, J. L., CAHAN, W. G., and NARDILLO, V. A. (1950): *J. Thorac. Surg.*, **20,** 169.
HARRINGTON, S. (1949): *Postgrad. Med. J.*, **6,** 6.
HOSOI, K. (1931): *Arch. Surg.*, **22,** 258.
JOHN, F., and ORMEA, F. (1951): *Arch. Derm. and Syph.*, **192,** 473.
KENT, E. M., BLADES, B., VALLE, A. B., and GRAHAM, E. A. (1944): *J. Thorac. Surg.*, **13,** 116.
MASSON, P., and SIMARD, C. (1930): *Amer. J. Path.*, **6,** 618.
MASSON, P. (1931): *Amer. J. Path.*, **8,** 367.
NAJEOTTE, J. (1932): " Penfield Wilder," Vol. 1. New York: Paul B. Hoeber Inc.

PRESTON, F. W., WALSH, W. S., and CLARKE, T. H. (1952): *Amer. Med. Ass. Arch. Surg.*, **6**, 813.
SCHARENBERG, K. (1952): *J. Neuropathy and Experimental Neurol.*, **11**, 257.
SMITH, R. W. (1849): Cited by Wilson, " Neurology," 1940, Vol. 2. Baltimore: Williams and Wilkins Co.
VICTOR, I. O., and PACK, G. T.: Cited by Godwin *et alia*.
VON RECKLINGHAUSEN (1882): Cited Ben W. Lichtenstein (1949), *Arch. Neurol. and Psychiatry*, **62**, 822.

REVIEWS OF BOOKS

Pneumoconiosis Abstracts, Volume I. Reprinted from the *Bulletin of Hygiene* for the years 1926 to 1938 inclusive. London: Sir Isaac Pitman and Sons Ltd. 1953. Pp. 347. 63s.

The abstracts in the *Bulletin of Hygiene* since its first publication in 1926 have gained a high reputation for accuracy and completeness, and it was an excellent idea to collect those relating to pneumoconiosis and allied subjects. The first volume, containing abstracts of articles published between 1926 and 1938, has just been issued and this is to be followed by another covering the period 1938-1950. It was particularly fortunate that the task of arranging and classifying the abstracts was entrusted to Dr. E. L. Middleton, the eminent authority on the pneumoconioses.

In the first volume the articles are arranged in twelve sections under such headings as silicosis, asbestosis, pneumoconiosis of coal workers and pneumoconiosis caused by dusts of vegetable origin. Other sections deal with dust sampling and measurement, preventive measures and legislation on pneumoconiosis. Within the sections the abstracts are arranged in chronological order, so that the development of ideas and research about each facet of the subject can be easily traced. For instance, those who are familiar only with the recent work on coal-miner's pneumoconiosis will be surprised to learn that much was known about its pathology and its clinical and X-ray features as early as 1931.

The list of contributors contains many distinguished names, none more so than that of Professor E. L. Collis, who has written more than 400 of the 736 articles contained in the volume. He has also contributed two long critical reviews of the literature of occupational dust diseases and silicosis both in 1931. To many of his abstracts are added shrewd comments, which enhance their usefulness and entertainment value. Other distinguished contributors, well known to students of tuberculosis, include Dr. C. Lillingston, the late Colonel S. Lyle Cummins and the late Dr. S. Roodhouse Gloyne.

Many abstracts deal with the relationship of tuberculosis, cancer, asthma and bronchitis to the pneumoconioses, thus making the collection valuable to those interested in general chest diseases as well as to students of the pneumoconioses.

The volume is attractively printed and contains a few illustrations, while the index, also prepared by Dr. E. L. Middleton, is comprehensive and accurate. There are only two criticisms to make. A minor one is that cross-references are given to pages in the *Bulletin of Hygiene* and not to pages of the volume of collected abstracts. And a major criticism is the high price of the book (3 guineas).

A. I. G. McLAUGHLIN.

Aspects of the Psychology of the Tuberculous. By GORDON F. DERNER, Ph.D. Published by Paul B. Hoeber. Medical Department of Harper Bros., New York. 1953. Pp. 119. Price 25s.

The author feels that tuberculosis deserves particular attention by psychiatrists because of the age-long belief that it attacked certain persons and gave

rise to very specific mental attitudes. A certain romantic aura has surrounded the victims of the disease which perhaps no other disease has acquired. A growing literature has accumulated which on the whole has given ambiguous results, and Wittkower's very careful study was perhaps the outstanding attempt to assign a psychopathic typology to this as to other alleged psychosomatic disorders.

This study deserves particular attention because, unlike most other researches, it attacks the problem by the use of standard tests and orderly interviews and questionnaires. Outstanding amongst these tests were the Institute of Education Research Reading Test (for Intelligence grading); the Rorscharch and Minnesota Personal Inventory (for the appraisal of personality peculiarities in depth).

What is most interesting to note is the care with which the attitudes over a wide field were assessed, and the freedom from psychological doctrinal bias. Individual interviewing did not appear to build up very striking personal pictures.

Overall it reveals what one has always suspected; that when the subject of body-mind relations is approached without any psychopathological bias, no specific mental reaction type emerges. Spes Phthisica remains an unsubstantiate myth. The Rorscharch revealed little more than unproductiveness, low affective levels and poor emotional output. This explodes the story that Tuberculosis is the febrile mother of creativeness. There is no doubt that frustrations, inadequacies, left unfaced, play a part in producing this and many other psychosomatic disorders. But the individual variations in character are so great that no psychological typology has so far been able to give to the tuberculous a specific psychodynamic structure.

EMANUEL MILLER.

Clinical Cardiology. Edited by FRANKLIN C. MASSEY. London: Baillière, Tindall and Cox 1953. Pp. 1,100. Price $13.50.

The contributors to this book are all from the United States and little mention is made of work from other countries. This is probably a pity, as even if Europeans do not generally put quite as much enthusiasm into the experimental approach, at least a great deal of clinical observations have been made on this side of the Atlantic. The word " clinical " does not appear to have quite the same connotation in this country. If the reader, therefore, wishes to read a book presenting symptoms and physical signs with a great amount of useful meaning wrung out of them, he will be disappointed. On the other hand, if he requires a first-rate exposition of the present position of cardiac surgery, hypotensive drugs, arteriosclerosis and applied physiology, he should buy the book at once.

The reviewer was a little disturbed to see such a sketchy medical review of congenital heart disease, where the impression is given that the physician's main rôle is in the use of investigational apparatus. However, in the succeeding chapter the surgical applications are so brilliantly put by surgeons that it is a delight to read.

Two chapters stand out, the first on the anatomy of the heart and the other on cardiac radiology by Schwedel.

It is a new departure to give a thumbnail account of the life history of the chapter authors at the beginning of each chapter. This is what must be

meant by " personalised," and is a pleasant state of affairs even if the youth of such knowledgeable men is not a little humiliating to readers.

RAYMOND DALEY.

Sectional Radiography of the Chest. By Irving J. Kace, M.D. New York: Springer Publishing Co. Inc. 1953. Price £3.

This is a book which, including the Bibliography, only runs to one hundred and fifty-one pages. One hundred and nine of these are devoted to illustrations and their captions. Of the thirty-five pages to which the text is limited some twelve are taken up by the first chapter on " Principles and Methods." The main conclusion of this chapter is that adequate tomographs can be obtained by reasonably simple equipment, and this is a conclusion with which no one would quarrel. The author, however, supports this conclusion by numerous arguments some of which are, at least, questionable.

The most helpful chapters are undoubtedly the third and fourth on " Anatomy and Pathology," which together only run to some seventeen pages. It follows, therefore, that in such a limited space one can only expect to find a résumé of present knowledge as to the possibilities and indications for tomography in the diagnosis and control of treatment in diseases of the chest. It would appear, therefore, that this book is only intended for those who have had little or no experience in tomographic investigation of chest disease.

The book is profusely illustrated but the illustrations unfortunately are not of a very high order. This is probably accounted for, in part, by the actual printing of the illustrations and also by the fact that they are in the form of negative prints. There is no doubt that in the reproduction of X-ray films every stage leads to a loss of detail, detail which is so important in chest radiography. Had the author been content with positive prints much of this detail would have been preserved. In spite of this criticism it must be agreed that the majority of illustrations, though not pleasing, are adequate. There are, however, a certain number which might well have been omitted since it is impossible to recognise in them the features they are intended to show.

The bibliography is extensive and should be a help to all interested in tomography.

L. G. BLAIR.

Funktionelle Atmungstherapie. (Breathing-therapy from the point of function). By JULIUS PAROW. Stuttgart: Georg Thieme Verlag. 1953. Pp. 126. Price not listed.

In this small monograph the author concerns himself with his own views regarding the mechanics of breathing in the ideally normal patient and disordered breathing function in asthma. In the management of patients with asthma, a prolonged and systematic course of breathing exercises is outlined which, under the author's guidance, rivals in effect the usual antispasmodic remedies. Particular stress is laid on simultaneous re-education of spinal posture in order to combat the development of emphysema, which the author regards as a secondary effect of faulty spinal posture leading to dorsal kyphosis. Much of what is said is unorthodox and represents speculative reasoning, but the methods suggested deserve study.

Strahlenschutz und Sonstiger Arbeitsschutz bei der Medizinischen Anwendung von Roentgenstrahlen (Irradiation-protection and other work-safety measures in the medical application of Roentgen rays). By WILHELM ERNST. Stuttgart: Georg Thieme Verlag. 1953. Pp. 94. Price not listed.

This well-produced small manual outlines the protective measures against irradiation hazards as prescribed by law in Western Germany. The legal requirements are stipulated under clear headings and appear to offer adequate safeguards for the personnel installing and operating Roentgen plants. The illustrations of equipment and protective clothing are well produced.

L. CUDKOWICZ.

BOOKS RECEIVED

The following books have been received and reviews of some of them will appear in the subsequent issues:

X-Ray Diagnosis of Chest Diseases. By Coleman B. Rabin. London: Baillière, Tindall and Cox. 1954. Pp. xi+208 with 288 Illus. 91s. 6d. First Edition.

A Synopsis of Children's Diseases. By John Rendle-Short. London: Simpkin Marshall Ltd. Bristol: John Wright and Sons Ltd. 1954. Pp. 620. Illus.

Tuberculosis in Childhood and Adolescence. With special reference to the pulmonary forms of the disease. By F. J. Bentley, S. Grzybowski and B. Benjamin. London: The National Association for the Prevention of Tuberculosis, 1954. Pp. xii+259. 67 illus. 30s.

A Two-Year-Old goes to Hospital. A Scientific Film Record by James Robertson. Tavistock Publications Ltd. 1953.

Health Horizon. Winter 1953. N.A.P.T. Pp. 56 with Illus. Quarterly 2s. 6d.

Australasian Annals of Medicine, Vol. II, No. 2, 1953. Pp. 113-212+vii. Illus.

Los Angeles County-wide Chest X-Ray Survey of 1950. By Godias J. Drolet. Los Angeles: Tuberculosis Control Foundation. 1953.

Tuberculoses Oculaires et Tuberculoses Paraganglionnaires. Étude phtisiologique et applications thérapeutiques. L. Paufique and J. Brun. Paris: Masson et Cie. 1954. Pp. 186. Illus. 1·350 fr.

Manuel Pratique de Vaccination par le B.C.G. By R. Mande. Paris: Masson et Cie. 1954. Pp. 200. Illus. 950 fr.

Techniques des Tuberculino-Reactions et de la Vaccination par le B.C.G. By Dr. Courcoux, Andre Meyer and J. P. Nico. Paris: Masson et Cie. 1954. Pp. 80. 62 Illus. 700 fr.

Schichtbilder von Bronchialveranderungen bei der Lungentuberkulose. By H. Blaha. Georg Thieme Verlag. Pp. viii+113; 86 illus. D.M. 18.

Der Einfluk der antibiotischen und chemotherapeutischen und chemotherapeutischen Behandlung auf das morphologische Bild der abheilenden Tuberkulose. By H. Lüchtrath. Georg Thieme Verlag. Pp. 104. 42 illus. 1954. D.M. 15.

REPORTS

MINISTRY OF HEALTH

THE Minister of Health has received the Report of the Standing Advisory Committee on Cancer and Radiotherapy on the question of the relationship between smoking and lung cancer.

The Committee are of the opinion:

(1) It must be regarded as established that there is a relationship between smoking and cancer of the lung.

(2) Though there is a strong presumption that the relationship is causal, there is evidence that the relationship is not a simple one, since—

(*a*) the evidence in support of the presence in tobacco smoke of a carcinogenic agent causing cancer of the lung is not yet certain;

(*b*) the statistical evidence indicates that it is unlikely that the increase in the incidence of cancer of the lung is due entirely to increases in smoking;

(*c*) the difference in incidence between urban and rural areas and between different towns, suggest that other factors may be operating—*e.g.*, atmospheric pollution, occupational risks.

(3) Although no immediate dramatic fall in death rates could be expected if smoking ceased, since the development of lung cancer may be the result of factors operating over many years, and although no reliable quantitative estimates can be made of the effect of smoking on the incidence of cancer of the lung, it is desirable that young people should be warned of the risks apparently attendant on excessive smoking. It would appear that the risk increases with the amount smoked, particularly of cigarettes.

REPORT ON THE HEALTH OF BIRMINGHAM IN 1952

THIS report contains some very interesting observations on Tuberculosis by Dr. J. E. Geddes.

There has been a steady reduction in mortality since 1939 in all age groups, but a warning note is sounded that these figures of reduced mortality must foster every endeavour in tuberculosis control and must not be used to underestimate the present state of tuberculosis in the city, for there is no reason for complacency—in fact, the circumstances demand an intensification of endeavours in prevention and treatment.

Stress is laid on the concentration of mortality in the middle age groups, 45-64, especially in males.

Laxity in notification is greatly to be deplored when all of the circumstances in tuberculosis control demand a more vigorous, purposeful and immediate action. It is well to recall that notification converts the patient from a " focus of infection " into a " focus of prevention." The penalty exacted by carelessness in the notification of cases of " open " pulmonary tuberculosis can indeed be a heavy one.

Housing of the tuberculous, rehabilitation, vaccination by B.C.G., and hostels, are all noted, and it is urged that what is now necessary is: (*a*) an

extension of vaccination; (*b*) adequate housing of the tuberculous population to prevent the spread of familial infection; (*c*) constant and intensive endeavours in case finding; (*d*) adequate treatment to fortify efforts in prevention, and a " half-way house " (hostel) to sustain the efforts of the health and hospital authorities.

ANNUAL REPORT OF THE MEDICAL OFFICER OF HEALTH, CITY OF GLASGOW, 1952

Dr. Stuart Laidlaw, in the preface to his Annual Report, makes the following observations in relation to Tuberculosis:

Probably no aspect of the Health Service has been more fully discussed in the press and in conference than the tuberculosis service. It is difficult to assess accurately the present position, for during the past six years tremendous developments have taken place in the treatment of this disease both by chemotherapy and by advances in pulmonary surgery. These developments have resulted in a marked diminution in the death rates at all ages. Unfortunately, no such decrease has occurred in the number of pulmonary cases notified in 1952, which totalled 2,264, an increase of 57 over the previous year and 614 in excess of the average number for the quinquennium 1935-39. Despite the large number of new notifications in recent years, the number of hospital and sanatorium beds has remained relatively static, and much treatment has required to be carried out in the patients' own homes. The principal reason for the lack of hospital accommodation is, of course, the shortage of nurses, and it would appear that the time is long overdue for a system of secondment of general nurses in training to the tuberculosis service.

The Health and Welfare Department is making a valuable contribution towards the solution of the tuberculosis problem by (*a*) further extending the municipal B.C.G. scheme to cover not only contacts but school leavers; (*b*) conducting one of the mass radiography units and thus assisting in the early detection of new cases; (*c*) increasing the number of tuberculosis health visitors to assist in the clinic work and carry out vital domiciliary duties; (*d*) providing a home help section specially devoted to the home care of tuberculous families; and (*e*) rehousing overcrowded families in which a case of open tuberculosis exists. It is hoped in these ways to effect a reduction in the number of new cases, especially among adolescents. Nevertheless, preventive workers feel that since the transfer of the hospital and clinic services to the Regional Hospital Board insufficient attention is being paid to the infectivity of this disease. It is indisputable that the clinical work is of a high standard, but there is a tendency to neglect the large number of chronically infectious persons from whom the majority of new cases arise. If early control of tuberculosis is to be achieved, some method of segregating the persistently infectious cases must be evolved.

REPORT OF THE COUNTY MEDICAL OFFICER FOR THE COUNTY COUNCIL OF THE WEST RIDING OF YORKSHIRE FOR 1952

The Annual Report for 1952 deals with the social aspects of some pulmonary diseases other than Tuberculosis which are of particular interest, viz.:

Cancer of the Lung

The great increase in the mortality figures from cancer of the lung has been the subject of investigation and speculation as to cause, not only in this country

but abroad, for a number of years. Of late it has gained more prominence on account of continued increasing mortality and because statistical correlation has been revealed between the condition and tobacco smoking which have been made much of in the lay press. Statistical correlation in itself is not direct evidence that tobacco smoking can be a cause of lung cancer.

There is controversy as to whether there is a real increase in mortality due to cancer of the lung or whether all or part can be attributed to improved methods of diagnosis. The deaths are taking place, however, and bid fair to exceed those from respiratory tuberculosis in years to come. The following figures for the West Riding Administrative County can be quoted as an example, but it should be borne in mind that they are only a reflection of a state of affairs in no way peculiar to the Administrative County:

	Number of deaths from:	
Year	*Cancer of the lung*	*Tuberculosis of respiratory system*
1950 ..	337	404
1951 ..	360	373
1952 ..	395	256

An Investigation into the Evolution of Chronic Bronchitis, under the general direction of Professor Stuart-Harris

An investigation into probable origins of those chronic chest diseases which usually terminate in heart failure is being conducted from the Department of Medicine at Sheffield University. Collaboration between local Health Authority medical staff and several General Practitioners as well as a large number of Health Visitors should make the future of this investigation of considerable interest. The pattern of the enquiry is now established, and Professor Stuart-Harris has obtained enough information to decide future action. Volunteers have been submitted to a searching clinical examination and the investigation is to spread out to include each member of the volunteer's family. The children are to be clinically examined and the Health Visitors will be extending their enquiries to the more detailed family circumstances.

NOTES AND NOTICES

THE THORACIC SOCIETY

THE Thoracic Society held their Spring Meeting at the Royal College of Surgeons on March 5 and 6.

Among the subjects under discussion were:

"Developmental Defects in the Lungs," opened by Mr. Peter Jones and Dr. D. M. Pryce; "Dyspnœa," opened by Professor R. V. Christie; "Intra-thoracic Actinomycosis," opened by Mr. M. Bates and Mr. G. Cruickshank, and "The Site of Origin of Cases of Bronchial Carcinoma," opened by Dr. H. Spencer and Dr. J. B. Walter. Short communications were read on:

"Acute Disseminated Histoplasmosis with a Report of a Case occurring in England." Dr. F. C. Poles.

"Studies in the Effect of Atelectasis of the Lung on the Local Progress of Pulmonary Tuberculosis." Mr. L. J. Temple.

"Intra-thoracic Duplications of the Bowel arising from the Foregut." Mr. J. T. Chesterman.

"The Assessment of Lung Function before and after Pneumonectomy for Bronchial Carcinoma." Dr. J. H. Friend.

"Skin Sensitivity Tests in Sarcoidosis." Dr. J. Dawson.

"The Clinical Application of Simultaneous Multisection Tomography in Intra-thoracic Disease." Dr. G. Simon.

An Exhibition of Specimens and Radiograms was on view during the meeting.

N.A.P.T.

THE National Association for the Prevention of Tuberculosis has published a leaflet on B.C.G. vaccination, a word to the parents from the Medical Officer of Health. In view of the extension of the Ministry of Health's B.C.G. vaccination scheme to 13-year-old school children, this is particularly valuable and is presented in a clear and lucid manner for the layman.

INTERNATIONAL CONGRESS FOR THE STUDY OF DISEASES OF THE BRONCHI

THIS congress will be held in Geneva on June 5 and 6, 1954.

The following subjects are under discussion: Blood Supply to the Bronchi, Bronchial Adenoma, Surgical Treatment of Bronchiectasis.

Further particulars can be obtained from Professor A. Montandon, Clinique universitaire d'Orl, Hôpital cantonal, Geneva.

NATIONAL TUBERCULOSIS ASSOCIATION OF AMERICA

THE National Tuberculosis Association will observe its fiftieth anniversary at a meeting in Atlantic City, N.J., the week of May 17-21.

Medical sessions for the period of the meeting are being planned by a committee of the N.T.A.'s medical section, the American Trudeau Society, and will cover latest developments in the field of chest diseases. There will be a number of seminars and panel discussions as well as sessions at which scientific papers will be presented.

AMERICAN COLLEGE OF CHEST PHYSICIANS

THE third International Congress on Diseases of the Chest will be held in Barcelona on October 4 to 8, 1954.

The subjects under discussion include Thoracic Surgery, Pulmonary Tuberculosis, Cancer of the Lung, Disease of the Pleura, Mediastinum, Œsophagus, Pericardium, Heart, Great Vessels and Diaphragm.

The Congress is being held under the patronage of the Spanish Government.

Further particulars can be obtained from the General Secretary of the Congress, Dr. A. Caralps, Corcega, 393, 4°.1ª. Barcelona, Spain.

The official languages of this Congress are: English, French, German and Spanish.